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Signed Stephen Hordley.

Dated 26 November 2003

Patents Form 1/77

Patents Act 1977
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The Patent Office

Cardiff Road
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South Wales
NP10 8QQ

1. Your reference — P15830-GB

2. Patent application number *(The Patent Office will fill in this part)* — 0326148.4 — 7 NOV 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ELI LILLY AND COMPANY,
LILLY CORPORATE CENTER,
INDIANAPOLIS,
INDIANA 46285, USA

Patents ADP number *(if you know it)* 428904002

If the applicant is a corporate body, give the country/state of its incorporation — STATE OF INDIANA, U.S.A.

4. Title of the invention — MORPHOLINE DERIVATIVES

5. Name of your agent *(if you have one)* — KINGSBURY, Oliver William

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

EUROPEAN PATENT OPERATIONS,
LILLY RESEARCH CENTRE,
ERL WOOD MANOR,
SUNNINGHILL ROAD,
WINDLESHAM,
SURREY, GU20 6PH, UK

Patents ADP number *(if you know it)* 73056180 01 TH

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

YES

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	
Description	86
Claim(s)	9
Abstract	1
Drawing(s)	0

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	Cover Letter

11. I/We request the grant of a patent on the basis of this application.

Signature

Date 10 Nov 2003

12. Name and daytime telephone number of person to contact in the United Kingdom

KINGSBURY, Oliver William

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Notes

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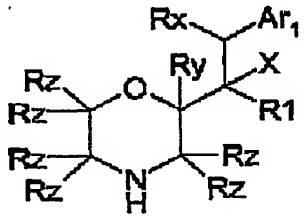
MORPHOLINE DERIVATIVES

This invention relates to novel morpholine compounds, and to their use in selectively inhibiting norepinephrine reuptake.

Selective inhibition of norepinephrine reuptake is a relatively new mode of action for the treatment of affective disorders. Norepinephrine appears to play an important role in the disturbances of vegetative function associated with affective, anxiety and cognitive disorders. Atomoxetine hydrochloride is a selective inhibitor of norepinephrine reuptake, and is marketed for the treatment of attention deficit hyperactivity disorder (ADHD). Reboxetine is also a selective norepinephrine reuptake inhibitor, and is marketed for the treatment of depression. WO99/15177 discloses the use of Reboxetine to treat ADHD and WO01/01973 discloses the use of S,S-Reboxetine to treat *inter alia* ADHD.

According to the present invention there is provided a compound of formula (I)



(I)

wherein,

X is OH, C1-C4 alkoxy, NH_2 or NH(C1-C4 alkyl);

Rx is H or C1-C4 alkyl;

Ry is H or C1-C4 alkyl;

each Rz group is independently H or C1-C4 alkyl, with the proviso that not more than 3 Rz groups may be C1-C4 alkyl;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6

cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C2-C6 alkenyl (optionally substituted with 1, 2 or 3 halogen atoms); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; C4-C7 cycloalkylalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH_2Ar2; and

Ar1 and Ar2 are each independently a phenyl ring or a 5- or 6-membered heteroaryl ring each of which is optionally substituted with 1, 2 or 3 substituents (depending upon the number of available substitution positions) each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy and/or with 1 substituent selected from pyridyl, thiophenyl, phenyl, benzyl and phenoxy each of which is optionally ring-substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R); and

each R is independently H or C1-C4 alkyl;

or a pharmaceutically acceptable salt thereof.

In the present specification the term "C1-C4 alkyl" means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms. Thus the term "C1-C4 alkyl" includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl.

In the present specification the term "C1-C4 alkoxy" means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms linked to the point of substitution by a divalent O radical. Thus the term "C1-C4

alkoxy" includes, for example, methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy.

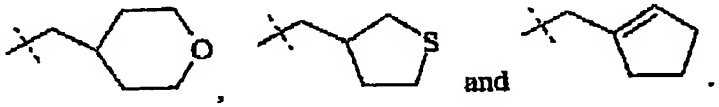
In the present specification the term "C1-C4 alkylthio" means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms linked to the point of substitution by a divalent S radical. Thus the term "C1-C4 alkylthio" includes, for example, methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio and tert-butylthio.

In the present specification the term "C3-C6 cycloalkyl" means a monovalent unsubstituted saturated cyclic hydrocarbon radical having from 3 to 6 carbon atoms. Thus the term "C3-C6 cycloalkyl" includes, for example, cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl.

In the present specification the term "C4-C7 cycloalkylalkyl" means a monovalent unsubstituted saturated cyclic hydrocarbon radical having from 3 to 6 carbon atoms linked to the point of substitution by a divalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having at least 1 carbon atom. Thus the term"C4-C7 cycloalkyl" includes, for example, cyclopropylmethyl, cyclopropylethyl, cyclobutylmethyl, cyclopentylmethyl and cyclohexylmethyl.

In the present specification the phrase "wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond" means that either (i) any two adjacent carbon atoms within a cycloalkyl ring may be linked by a double bond rather than a single bond (with the number of substituents on each carbon atom being reduced accordingly), or that (ii) one of any two adjacent C atoms within a cycloalkyl ring (and any substituents thereon) may be replaced by an oxygen or sulphur atom. Examples of groups encompassed by this phrase when used in conjunction with the term C3-C6 cycloalkyl include, for example:

Examples of groups encompassed by this phrase when used in conjunction with the term C4-C7 cycloalkylalkyl include, for example:



In the present specification the term "C2-C6 alkenyl" means a monovalent unsubstituted unsaturated straight-chain or branched-chain hydrocarbon radical having from 2 to 6 carbon atoms and containing at least one carbon-carbon double bond. Thus the term "C1-C4 alkenyl" includes, for example, ethenyl, propenyl, 2-methyl-2-propenyl and butenyl.

In the present specification the term "C3-C6 cycloalkoxy" means a monovalent unsubstituted saturated cyclic hydrocarbon radical having from 3 to 6 carbon atoms in the ring linked to the point of substitution by a divalent O radical. Thus the term "C3-C6 cycloalkoxyl" includes, for example, cyclopropoxy.

In the present specification the term "C1-C4 alkylsulfonyl" means a monovalent unsubstituted saturated straight-chain or branched-chain hydrocarbon radical having from 1 to 4 carbon atoms linked to the point of substitution by a divalent SO_2 radical. Thus the term "C1-C4 alkylsulfonyl" includes, for example, methylsulfonyl.

In the present specification terms similar to the above definitions specifying different numbers of C atoms take an analogous meaning.

In the present specification the term "halo" or "halogen" means F, Cl, Br or I.

In the present specification the term "phenoxy" means a monovalent unsubstituted phenyl radical linked to the point of substitution by a divalent O radical.

In the present specification the term "5-membered heteroaryl ring" means a 5-membered aromatic ring including one or more heteroatoms each independently selected from N, O and S. Preferably there are not more than three heteroatoms in total in the ring. More preferably there are not more than two heteroatoms in total in the ring. More preferably there is not more than one heteroatom in total in the ring. The term includes, for example, the groups thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, thiophenyl, furanyl, pyrrolyl, imidazolyl, triazolyl, oxadiazolyl and thiadiazolyl.

"Thiazolyl" as used herein includes 2-thiazolyl, 4-thiazolyl and 5-thiazolyl.

"Isothiazolyl" as used herein includes 3-isothiazolyl, 4-isothiazolyl, and 5-isothiazolyl.

"Oxazolyl" as used herein includes 2-oxazolyl, 4-oxazolyl and 5-oxazolyl.

"Isoxazolyl" as used herein includes 3-isoxazolyl, 4-isoxazolyl, and 5-isoxazolyl.

"Thiophenyl" as used herein includes 2-thiophenyl and 3-thiophenyl.

"Furanyl" as used herein includes 2-furanyl and 3-furanyl.

"Pyrrolyl" as used herein includes 2-pyrrolyl and 3-pyrrolyl.

"Imidazolyl" as used herein includes 2-imidazolyl and 4-imidazolyl.

"Triazolyl" as used herein includes 1-triazolyl, 4-triazolyl and 5-triazolyl.

"Oxadiazolyl" as used herein includes 4- and 5-(1,2,3-oxadiazolyl), 3- and 5-(1,2,4-oxadiazolyl), 3-(1,2,5-oxadiazolyl), 2-(1,3,4-oxadiazolyl).

"Thiadiazolyl" as used herein includes 4- and 5-(1,2,3-thiadiazolyl), 3- and 5-(1,2,4-thiadiazolyl), 3-(1,2,5-thiadiazolyl), 2-(1,3,4-thiadiazolyl).

In the present specification the term "6-membered heteroaryl ring" means a 6-membered aromatic ring including one or more heteroatoms each independently selected from N, O and S. Preferably there are not more than three heteroatoms in total in the ring. More preferably there are not more than two heteroatoms in total in the ring. More preferably there is not more than one heteroatom in total in the ring. The term includes, for example, the groups pyridyl, pyrimidyl, pyrazinyl, pyridazinyl and triazinyl.

"Pyridyl" as used herein includes 2-pyridyl, 3-pyridyl and 4-pyridyl.

"Pyrimidyl" as used herein includes 2-pyrimidyl, 4-pyrimidyl and 5-pyrimidyl.

"Pyrazinyl" as used herein includes 2-pyrazinyl and 3-pyrazinyl.

"Pyridazinyl" as used herein includes 3-pyridazinyl and 4-pyridazinyl.

"Triazinyl" as used herein includes 2-(1,3,5-triazinyl), 3-, 5- and 6-(1,2,4-triazinyl) and 4- and 5-(1,2,3-triazinyl).

In the present specification the term "*ortho*" refers to a position on the Ar1 aromatic ring which is adjacent to the position from which Ar1 links to the rest of the compound of formula (I).

In a preferred embodiment of the present invention, X is OH, C1-C4 alkoxy, or NH_2. More preferably, X is OH or NH_2. Most preferably X is OH.

In a preferred embodiment of the present invention, Rx is H or methyl. Most preferably Rx is H.

In a preferred embodiment of the present invention, Ry is H or methyl. Most preferably Ry is H.

In a preferred embodiment of the present invention, each Rz group is independently H or methyl, with the proviso that not more than 3 Rz groups may be methyl. Most preferably, each Rz is H.

In a preferred embodiment of the present invention, R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy). More preferably, R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent

selected from C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), cyano and hydroxy). More preferably, R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms). More preferably, R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms). Examples of specific identities for R1 within this embodiment include methyl, ethyl, iso-propyl, iso-butyl, 3,3,3-trifluoropropyl and 4,4,4-trifluorobutyl.

In a preferred embodiment of the present invention, R1 is C2-C6 alkenyl (optionally substituted with 1, 2 or 3 halogen atoms).

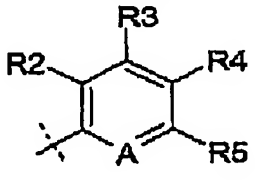
In a preferred embodiment of the present invention, R1 is C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond. More preferably, R1 is C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond. More preferably, R1 is C3-C6 cycloalkyl wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond. Examples of specific identities for R1 within this embodiment include cyclopropyl, cyclopentyl and tetrahydropyranyl (in particular tetrahydro-2H-pyran-4-yl).

In a preferred embodiment of the present invention, R1 is C4-C7 cycloalkylalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond.

In a preferred embodiment of the present invention, R1 is CH_2Ar2 wherein Ar2 is as defined above. More preferably, R1 is CH_2Ar2 wherein Ar2 is a phenyl ring or a pyridyl (preferably 2-pyridyl) ring each of which may be substituted with 1, 2 or 3 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy.

More preferably, R1 is CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted in the manner described in the preceding sentence. More preferably, R1 is CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy. Examples of specific identities for R1 within this embodiment include phenylmethyl and (2-methoxy-phenyl)methyl.

In a preferred embodiment of the present invention, Ar1 is a phenyl ring or a 5- or 6-membered heteroaryl ring; each of which is substituted in the *ortho* position with a substituent selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo, hydroxy, pyridyl, thiophenyl, phenyl, benzyl and phenoxy, each of which *ortho* substituents is optionally ring-substituted (where a ring is present) with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R; and each of which is (in addition to *ortho* substitution) optionally further substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy. More preferably, Ar1 is a phenyl ring or a pyridyl (preferably 2-pyridyl) ring each of which is substituted and optionally further substituted in the manner described in the preceding sentence. More preferably, Ar1 is a group of the formula (a):

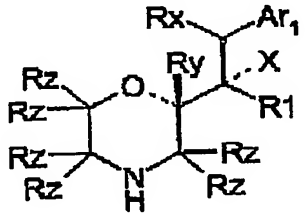


(a)

wherein,

A is N or CR6 (preferably CR6); R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo, hydroxy, pyridyl, thiophenyl, phenyl (optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), or C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms)) or phenoxy (optionally substituted with 1, 2 or 3 halogen atoms); R3 is H; R4 is H; R5 is H, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo or hydroxy; and R6 (if present) is H. More preferably, Ar1 is a group of the formula (a) wherein, A is CR6; R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms) or phenyl (optionally substituted with 1, 2 or 3 fluorine atoms); R3 is H; R4 is H; R5 is H or F; and R6 is H. Examples of specific identities for Ar1 include 2-methoxy-phenyl, 2-ethoxy-phenyl, 2-trifluoromethoxy-phenyl, 2-phenyl-phenyl, 2-(3-fluoro-phenyl)-phenyl, 2-methoxy-5-fluoro-phenyl and 2-phenyl-5-fluoro-phenyl.

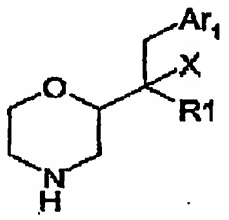
It will be appreciated that a compound of formula (I) above will possess at least two asymmetric carbon atoms. In the present specification, where a structural formula does not specify the stereochemistry at one or more chiral centres, it encompasses all possible stereoisomers and all possible mixtures of stereoisomers (including, but not limited to, racemic mixtures), which may result from stereoisomerism at each of the one or more chiral centers. In a preferred embodiment of the present invention, there is provided a compound of formula (II)



(II)

wherein, X, Rx, Ry, Rz, R1 and Ar1 are as defined for formula (I) above; or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the present invention, there is provided a compound of formula (III)



(III)

wherein, X, R1 and Ar1 are as defined for formula (I) above; or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the present invention, there is provided a compound of formula (III) wherein

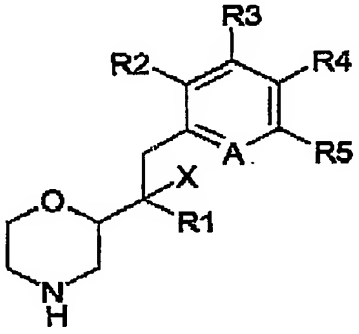
X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH_2Ar2 wherein Ar2 is a phenyl ring or a pyridyl (preferably 2-pyridyl) ring each of which may be substituted with 1, 2 or 3 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy; and

Ar1 is a phenyl ring or a 5- or 6-membered heteroaryl ring; each of which is substituted in the *ortho* position with a substituent selected from C1-C4 alkyl (optionally substituted

with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo, hydroxy, pyridyl, thiophenyl, phenyl, benzyl and phenoxy, each of which *ortho* substituents is optionally ring-substituted (where a ring is present) with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R; and each of which is (in addition to *ortho* substitution) optionally further substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy; or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the present invention, there is provided a compound of formula (IV)



(IV)

wherein,

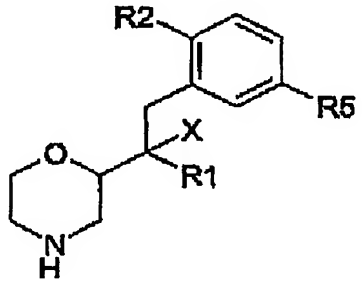
X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), cyano, and hydroxy); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy)

wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond; or CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted with 1, 2 or 3 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy;

A is N or CR6 (preferably CR6); R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo, hydroxy, pyridyl, thiophenyl, phenyl (optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), or C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms)) or phenoxy (optionally substituted with 1, 2 or 3 halogen atoms); R3 is H; R4 is H; R5 is H, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo or hydroxy; and R6 (if present) is H; or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the present invention, there is provided a compound of formula (V)



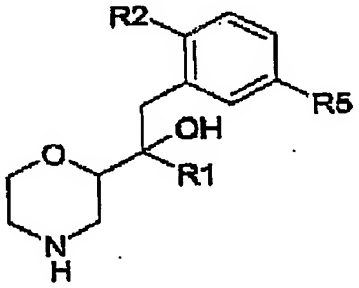
(V)

wherein,

X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkyl wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond or CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy;
R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms) or phenyl (optionally substituted with 1, 2 or 3 fluorine atoms); and R5 is H or F; or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the present invention, there is provided a compound of formula (VI)



(VI)

wherein,
R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms) or C3-C6 cycloalkyl wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond;
R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms) or phenyl (optionally substituted with 1, 2 or 3 fluorine atoms); and R5 is H or F; or a pharmaceutically acceptable salt thereof.

Specific embodiments of the present invention include the compounds 1-[1,1'-biphenyl]-2-yl-2-morpholin-2-ylpropan-2-ol,

1-[5-fluoro-2-(methyloxy)phenyl]-2-morpholin-2-ylbutan-2-ol,
2-morpholin-2-yl-1-{2-[(trifluoromethyl)oxy]phenyl}butan-2-ol,
1-[1,1'-biphenyl]-2-yl-2-morpholin-2-ylbutan-2-ol,
1-[5-fluoro-2-(methyloxy)phenyl]-3-methyl-2-morpholin-2-ylbutan-2-ol,
3-methyl-1-[(2-methyloxy)phenyl]-2-morpholin-2-ylbutan-2-ol,
1-[(2-ethyloxy)phenyl]-3-methyl-2-morpholin-2-ylbutan-2-ol,
3-methyl-2-morpholin-2-yl-1-{2-[(trifluoromethyl)oxy]butan-2-ol,
1-[1,1'-biphenyl]-2-yl-3-methyl-2-morpholin-2-ylbutan-2-ol,
1-(4-fluoro[1,1'-biphenyl]-2-yl)-3-methyl-2-morpholin-2-ylbutan-2-ol,
1-[5-fluoro-2-(methyloxy)phenyl]-4-methyl-2-morpholin-2-yl-pentan-2-ol,
1-[2-(ethyloxy)phenyl]-4-methyl-2-morpholin-2-ylpentan-2-ol,
4-methyl-2-morpholin-2-yl-1-{2[trifluoromethyl) oxy]phenyl}pentan-2-ol,
1-[1,1'-biphenyl]-2-yl-4-methyl-2-morpholin-2-ylpentan-2-ol,
1-(4-fluoro[1,1'-biphenyl]-2-yl)-4-methyl-2-morpholin-2-ylpentan-2-ol,
1-cyclopentyl-2-[5-fluoro-2-(methyloxy)phenyl]-1-morpholin-2-ylethanol,
1-cyclopentyl-2-[2-(ethyloxy)phenyl]-1-morpholin-2-ylethanol,
1-cyclopentyl-1-morpholin-2-yl-2-{2-[(trifluoromethyl)oxy] phenyl} ethanol,
2-[1,1'-biphenyl]-2-yl-1-cyclopentyl-1-morpholin-2-ylethanol,
1-cyclopentyl-2-(4-fluoro[1,1'-biphenyl]-2-yl)-1-morpholin-2-ylethanol,
2-[5-fluoro-2-methyloxy)phenyl]-1-morpholin-2-yl-1-tetrahydro-2H-pyran-4-ylethanol,
1-morpholin-2-yl-1-tetrahydro-2H-pyran-4-yl-2-{2-[(trifluoromethyl)oxy]
phenyl}ethanol,
2-[1,1'-biphenyl]-2-yl-1-morpholin-2-yl-1-tetrahydro-2H-pyran-4-ylethanol,
2-(3'-fluoro-biphenyl-2-yl)-1-morpholin-2-yl-1-(tetrahydro-pyran-4-yl)-ethanol,
5,5,5-trifluoro-1-(5-fluoro-2-methoxy-phenyl)-2-morpholin-2-yl-pentan-2-ol,
5,5,5-trifluoro-2-morpholin-2-yl-1-(2-trifluoromethoxy-phenyl)-pentan-2-ol,
1-[1,1'-biphenyl]-2-yl-5,5,5-trifluoro-2-morpholin-2-ylpentan-2-ol,
6,6,6-trifluoro-1-[5-fluoro-2-(methyloxy)phenyl]-2-morphol-2-ylhexan-2-ol,
1-[1,1'-biphenyl]-2-yl-6,6,6-trifluoro-2-morpholin-2-yl]hexan-2-ol,
1-cyclopropyl-2-[-2-(methyloxy)phenyl]-1-morpholin-2-ylethanol,
1-cyclopropyl-2-[-2-(ethyloxy)phenyl]-1-morpholin-2-ylethanol,

2-[1,1'-biphenyl]-2-yl-1-cyclopropyl-1-morpholin-2-ylethanol,
1,3-bis-(2-methoxy-phenyl)-2-morpholin-2-yl-propan-2-ol,
1-(2-methoxy-benzyl)-2-(2-methoxy-phenyl)-1-morpholin-2-yl-ethylamine,
2-morpholin-2-yl-1,3-diphenyl-propan-2-ol
and pharmaceutically acceptable salts thereof.

The compounds of the present invention are inhibitors of norepinephrine reuptake. Biogenic amine transporters control the amount of biogenic amine neurotransmitters in the synaptic cleft. Inhibition of the respective transporter leads to a rise in the concentration of that neurotransmitter within the synaptic cleft. Compounds of formula (I) and their pharmaceutically acceptable salts preferably exhibit a K_i value less than 600nM at the norepinephrine transporter as determined using the scintillation proximity assay described below. More preferred compounds of formula (I) and their pharmaceutically acceptable salts exhibit a K_i value less than 100nM at the norepinephrine transporter. More preferred compounds of formula (I) and their pharmaceutically acceptable salts exhibit a K_i value less than 50nM at the norepinephrine transporter. Especially preferred compounds of formula (I) and their pharmaceutically acceptable salts exhibit a K_i value less than 20nM at the norepinephrine transporter. Preferably, compounds of the present invention selectively inhibit the norepinephrine transporter relative to the serotonin and dopamine transporters by a factor of at least five, more preferably by a factor of at least ten using the scintillation proximity assays described below.

In addition, the compounds of the present invention are preferably acid stable. Advantageously, they have a reduced interaction (both as substrate and inhibitor) with the liver enzyme Cytochrome P450 (CYP2D6). That is to say, they preferably exhibit less than 75% metabolism via the CYP2D6 pathway according to the CYP2D6 substrate assay described below and they preferably exhibit an IC50 of >6μM according to the CYP2D6 inhibitor assay described below.

In view of their pharmacological activity, the compounds of the present invention are indicated for the treatment of disorders of the central and/or peripheral nervous system, in particular, disorders associated with norepinephrine dysfunction in mammals, especially humans, including children, adolescents and adults.

The term "norepinephrine dysfunction" as used herein refers to a reduction in the amount of norepinephrine neurotransmitter within the synaptic cleft below that which would be considered to be normal or desirable for a species, or an individual within that species. Thus the phrase "disorders associated with norepinephrine dysfunction in mammals" refers to disorders which are associated with a reduction in the amount of norepinephrine neurotransmitter within the synaptic cleft below that which would be considered to be normal or desirable for the mammalian species, or an individual within the species, in question. Disorders associated with norepinephrine dysfunction in mammals include, for example, nervous system conditions selected from the group consisting of an addictive disorder and withdrawal syndrome, an adjustment disorder (including depressed mood, anxiety, mixed anxiety and depressed mood, disturbance of conduct, and mixed disturbance of conduct and mood), an age-associated learning and mental disorder (including Alzheimer's disease), alcohol addiction, anorexia nervosa, apathy, an attention-deficit disorder (ADD) due to general medical conditions, attention-deficit hyperactivity disorder (ADHD) including the predominantly inattentive type of ADHD and the predominantly hyperactive-impulsive type of ADHD, bipolar disorder, bulimia nervosa, chronic fatigue syndrome, chronic or acute stress, cognitive disorders including mild cognitive impairment (MCI) and cognitive impairment associated with schizophrenia (CIAS), communication disorders (including stuttering, expressive language disorder, mixed receptive-expressive language disorder, phonological disorder and communication disorder not otherwise specified), conduct disorder, cyclothymic disorder, dementia of the Alzheimers type (DAT), depression (including adolescent depression and minor depression), dysthymic disorder, emotional dysregulation (including emotional dysregulation associated with ADHD, borderline personality disorder, bipolar disorder, schizophrenia, schizoaffective disorder and intermittent explosive disorder), fibromyalgia and other somatoform disorders (including somatization

disorder, conversion disorder, pain disorder, hypochondriasis, body dysmorphic disorder, undifferentiated somatoform disorder, and somatoform NOS), generalized anxiety disorder, hypotensive states including orthostatic hypotension, incontinence (i.e., stress incontinence, genuine stress incontinence, and mixed incontinence), an inhalation disorder, an intoxication disorder, learning disabilities (including developmental speech and language disorders (such as developmental articulation disorder, developmental expressive language disorder and developmental receptive language disorder), learning disorders (such as reading disorder, mathematics disorder, disorder of written expression and learning disorder not otherwise specified) and motor skills disorders (such as developmental coordination disorder)), mania, migraine headaches, neuropathic pain, nicotine addiction, obesity (i.e., reducing the weight of obese or overweight patients), obsessive compulsive disorders and related spectrum disorders, oppositional defiant disorder, pain including chronic pain, neuropathic pain and antinociceptive pain, panic disorder, peripheral neuropathy, post-traumatic stress disorder, premenstrual dysphoric disorder (i.e., premenstrual syndrome and late luteal phase dysphoric disorder), psoriasis, psychoactive substance use disorders, a psychotic disorder (including schizophrenia, schizoaffective and schizophreniform disorders), seasonal affective disorder, a sleep disorder (such as narcolepsy and enuresis), social phobia (including social anxiety disorder), a specific developmental disorder, selective serotonin reuptake inhibition (SSRI) "poop out" syndrome (i.e., wherein a patient who fails to maintain a satisfactory response to SSRI therapy after an initial period of satisfactory response), TIC disorders (e.g., Tourette's Disease), tobacco addiction and vascular dementia. The compounds of the present invention are particularly suitable for the treatment of attention deficit hyperactivity disorder, ADHD. The compounds of the present invention are also particularly suitable for the treatment of schizophrenia.

The term "treatment" as used herein refers to both curative and prophylactic treatment of disorders associated with norepinephrine dysfunction.

The compounds of the present invention are also indicated for the treatment of disorders which are ameliorated by an increase in the amount of norepinephrine neurotransmitter

within the synaptic cleft of a mammal above that which would be considered to be normal or desirable for the mammalian species, or an individual within the species, in question.

In another embodiment of the present invention, there is provided a pharmaceutical composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent, excipient or carrier.

In another embodiment of the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof for use in therapy.

In another embodiment of the present invention, there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an inhibitor of the reuptake of norepinephrine. Preferably such inhibition occurs within mammalian cells (including mammalian cell membrane preparations), especially those found within the central and/or peripheral nervous system. More preferably such inhibition occurs within the cells of the central nervous system of a mammal, especially a human, in need thereof.

In another embodiment of the present invention there is provided a compound of formula (I) or a pharmaceutically acceptable salt thereof for treating disorders associated with norepinephrine dysfunction in mammals.

In another embodiment of the present invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for inhibiting the reuptake of norepinephrine.

In another embodiment of the present invention, there is provided the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disorders associated with norepinephrine dysfunction in mammals.

In another embodiment of the present invention, there is provided a method for inhibiting the reuptake of norepinephrine in mammals comprising administering to a patient in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another embodiment of the present invention, there is provided a method for treating disorders associated with norepinephrine dysfunction in mammals comprising administering to a patient in need thereof an effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The present invention includes the pharmaceutically acceptable salts of the compounds of formula (I). Suitable salts include acid addition salts, including salts formed with inorganic acids, for example hydrochloric, hydrobromic, nitric, sulphuric or phosphoric acids, or with organic acids, such as organic carboxylic or organic sulphonic acids, for example, acetoxybenzoic, citric, glycolic, *o*- mandelic-l, mandelic-dl, mandelic d, maleic, mesotartaric monohydrate, hydroxymaleic, fumaric, lactobionic, malic, methanesulphonic, napsylic, naphthalenedisulfonic, naphtoic, oxalic, palmitic, phenylacetic, propionic, pyridyl hydroxy pyruvic, salicylic, stearic, succinic, sulfanilic, tartaric, 2-hydroxyethane sulphonic, toluene-p-sulphonic, and xinafoic acids.

The compounds of the present invention may be used as medicaments in human or veterinary medicine. The compounds may be administered by various routes, for example, by oral or rectal routes, topically or parenterally, for example by injection, and are usually employed in the form of a pharmaceutical composition.

Such compositions may be prepared by methods well known in the pharmaceutical art and normally comprise at least one active compound in association with a pharmaceutically acceptable diluent, excipient or carrier. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier or diluted by a carrier, and/or enclosed within a carrier which may, for example, be in the form of a capsule, sachet, paper or other container. Where the carrier serves as a diluent, it may be

solid, semi-solid, or liquid material which acts as a vehicle, excipient or medium for the active ingredient. Thus, the composition may be in the form of tablets, lozenges, sachets, cachets, elixirs, suspensions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, suppositories, injection solutions and suspensions and sterile packaged powders.

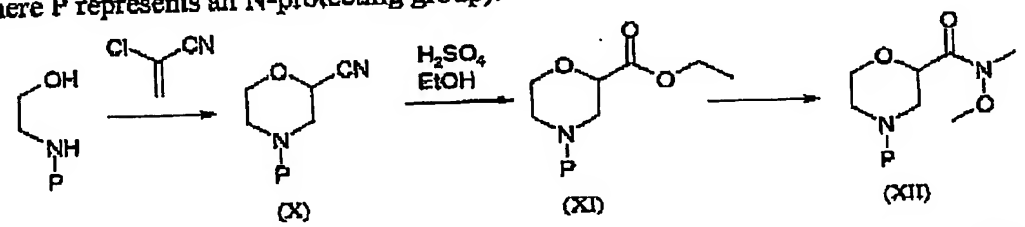
Some examples of suitable carriers are lactose, dextrose, vegetable oils, benzyl alcohols, alkylene glycols, polyethylene glycols, glycerol triacetate, gelatin, carbohydrates such as starch and petroleum jelly, sucrose sorbitol, mannitol, starches, gum acacia,calcium phosphate, alginates, tragacanth, gelatin, syrup, methyl cellulose, methyl- and propyl-hydrobenzoate, talc, magnesium stearate and mineral oil. The compounds of formula (I) can also be lyophilized and the lyophilizates obtained used, for example, for the production of injection preparations. The preparations indicated can be sterilized and/or can contain auxiliaries such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts for affecting the osmotic pressure, buffer substances, colourants, flavourings and/or one or more further active compounds, e.g. one or more vitamins. Compositions of the invention may be formulated so as to provide, quick, sustained or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a dosage unit form, each dosage unit containing from about 5 to about 500 mg, more usually about 25 to about 300 mg, of the active ingredient. The term "dosage unit form" refers to physically discrete units suitable as unitary doses for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier.

Compounds of the present invention may be prepared by conventional organic chemistry techniques. General schemes outlining the synthetic routes to compounds of the present invention are described below. For clarity, Rx, Ry and Rz are shown as H, however, it

will be appreciated that analogous methods could be applied for other possible identities of Rx, Ry and Rz.

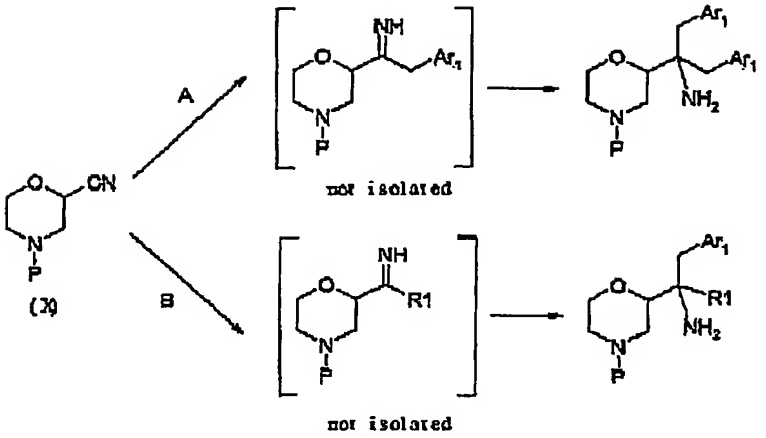
The key intermediates of formulae (X), (XI) and (XII) may be prepared as shown below (where P represents an N-protecting group):



(X) (XI) (XII)

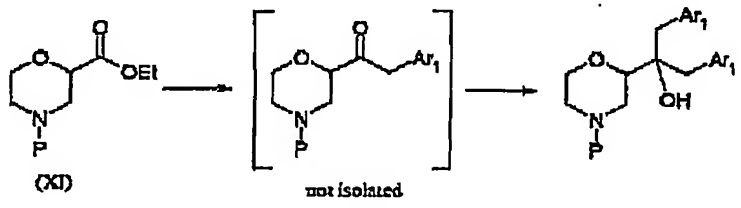
N-protected ethanolamine is reacted with 2-chloroacrylonitrile to give a Michael adduct which is then treated *in situ* with a base, such as potassium t-butoxide, to give a compound of formula (X). The compound of formula (X) may then be hydrolysed in H_2SO_4/ethanol to give the ester of formula (XI). This in turn may be converted into the Weinreb amide of formula (XII) by adding a solution of (XI) to a premixed solution of *N,N*-dimethylhydroxylamine and trimethylaluminium. Suitable N-protecting groups will be known to the person skilled in the art. Further information on suitable N-protecting groups is contained in the well known text "Protective Groups in Organic Synthesis", Theodora W. Greene and Peter G.M. Wuts, John Wiley & Sons, Inc., New York, 1999, pp.494-653. Benzyl is an especially preferred N-protecting group.

N-protected compounds of formula (I) wherein X is NH_2 may be prepared from compounds of formula (X) as shown below:



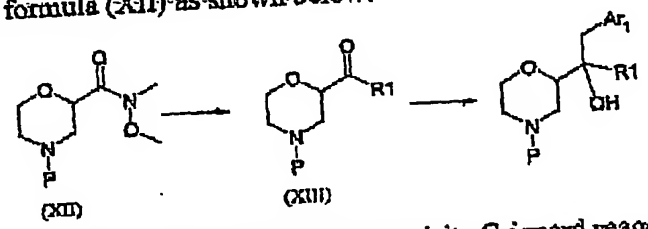
In route A the intermediate (X) is treated with an excess of the Grignard reagent Ar1CH_2MgBr to provide an N-protected compound of formula (I) wherein X is NH_2 and R1 is CH_2Ar2 wherein Ar2 = Ar1. In route B the intermediate (X) is treated with one equivalent of the Grignard reagent R1MgBr followed by one equivalent of the Grignard reagent Ar1CH_2MgBr to provide an N-protected compound of formula (I) wherein X is NH_2. Alternatively, the Grignard reagent Ar1CH_2MgBr may be added first followed by R1MgBr. Preferably, a Lewis acid such as titanium isopropoxide is added to the reaction mixture in between addition of the Grignard reagents (see Charette, A.B.; Gagnon, A; Janes, M; Mellon, C; Tetrahedron Lett, 1998, 39(29), 5147-5150 and Charette, A.B.; Gagnon, A; Tetrahedron: Asymmetry, 1999, 10(10), 1961-1968).

N-protected compounds of formula (I) wherein X is OH and R1 is CH_2Ar2 wherein Ar2 = Ar1 may be prepared from compounds of formula (XI) as shown below:



Intermediate (XI) is treated with an excess of the Grignard reagent Ar1CH_2MgBr to provide an N-protected compound of formula (I) wherein X is OH and R1 is CH_2Ar2 wherein Ar2 = Ar1.

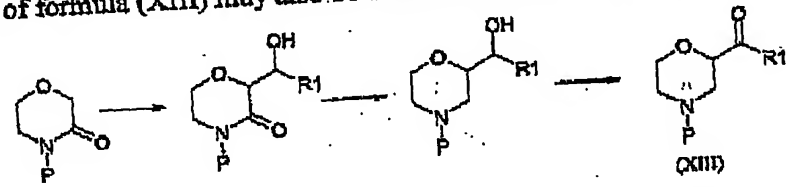
N-protected compounds of formula (I) wherein X is OH may be prepared from the Weinreb amide of formula (XII) as shown below:



(XII) (XIII)

To a solution of (XII) is added a solution of the requisite Grignard reagent R1MgBr to provide, on work up, a compound of formula (XIII). To a solution of the ketone of formula (XIII) is added a solution of the Grignard reagent Ar1CH2MgBr to provide an N-protected compound of formula (I) wherein X is OH.

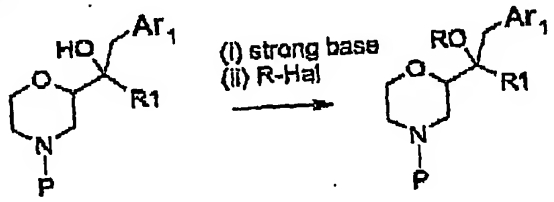
The ketones of formula (XIII) may also be obtained via a different route as shown below:



(XIII)

A solution of N-protected morpholinone is treated with a strong base such as lithium diisopropylamide. To this solution is added an aldehyde R1CHO. Reduction of the morpholine carbonyl group using, for example, borane-THF complex followed by oxidation of the alcohol using, for example, Swern oxidation conditions, provides a compound of formula (XIII) which can be reacted onward as described in the previous scheme to provide an N-protected compound of formula (I) wherein X is OH.

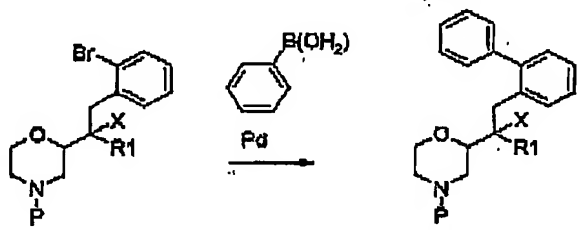
N-protected compounds of the present invention wherein X is C1-C4 alkoxy, may be synthesized by standard alkylation of the N-protected compounds of formula (I) wherein X=OH as shown below:



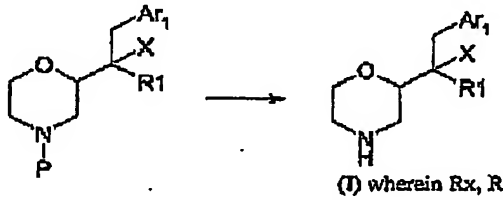
Suitable strong bases will be known to the person skilled in the art and include, for example, sodium hydride. Similarly, suitable alkylating agents will be known to the person skilled in the art and include, for example, C1-C4 alkyl halides such as methyl iodide.

N-protected compounds of the present invention wherein X is NH(C1-C4 alkyl), may be synthesized by treatment of a compound of formula (I) wherein X = NH_2 under reductive alkylating conditions or using suitable alkylating agents known to the person skilled in the art including, for example, C1-C4 alkyl halides such as methyl iodide.

N-protected compounds of the present invention may be elaborated upon using standard organic chemistry to provide further N-protected compounds of the present invention. For example, organometallic type couplings between an Ar1-Br derivative and a phenylboronic acid as shown below can provide Ar1-phenyl derivatives.



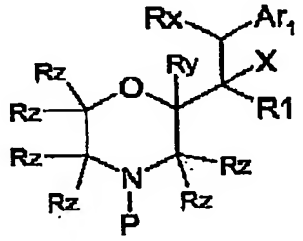
Compounds of formula (I) may be obtained by deprotection of the N-protected intermediates as shown below:



(I) wherein Rx, Ry and Rz = H

Further information on suitable deprotection methods is contained in the well known text "Protective Groups in Organic Synthesis" referenced above.

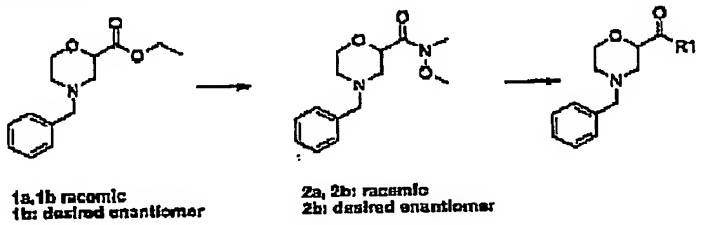
Thus, in another embodiment of the present invention there is provided a process for the preparation of compounds of formula (I) comprising the step of deprotecting a compound of the formula (XIV)



(XIV)

wherein P represents an N-protecting group and all other variables are as defined for formula (I) above, to provide a compound of formula (I), optionally followed by the step of forming a pharmaceutically acceptable salt.

Examples of compounds of the present invention may be prepared by conventional organic chemistry techniques from *N*-benzyl-morpholine-2-carboxylic acid ethyl ester **1** as outlined in **Scheme 1**.



Scheme 1

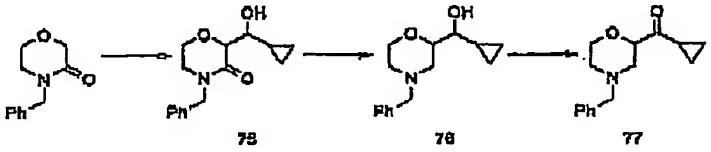
Conversion of **1** into Weinreb amide **2** followed by treatment with a suitable Grignard reagent leads to ketones listed in **Table 1.**

R1	Number
methyl	3
ethyl	4
isopropyl	5
isobutyl	6
cyclopentyl	7
tetrahydropyranyl	8

3,3,3-trifluoropropyl	9
4,4,4-trifluorobutyl	10
cyclopropyl	77

Table 1

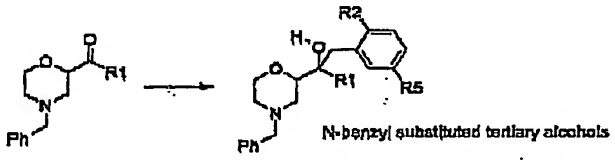
Cyclopropyl-substituted ketone **77** may alternatively be obtained from N-benzyl morpholinone as outlined in **Scheme 4**.



Scheme 4

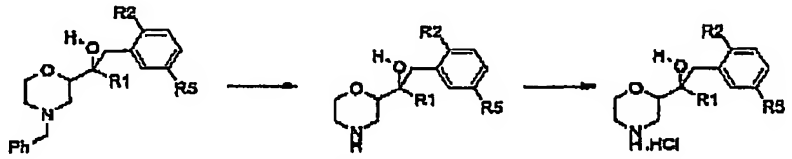
Treatment of the benzyl-morpholinine with a strong base such as lithium diisopropylamide followed by addition of cyclopropyl methylaldehyde gives **75**. Reduction of **75** with, for example, borane-THF complex gives **76**. Addition of a solution of **76** to a pre-mixed solution of dimethylsulfoxide and oxalyl chloride provides **77**.

Reaction of ketones listed in **Table 1** with a suitably substituted benzyl Grignard reagent gives N-benzyl substituted tertiary alcohols listed in **Table 2** as outlined in **Scheme 2**.



Scheme 2

Debenzylation and salt formation as detailed in **Scheme 3** leads to the tertiary alcohol salts listed in **Table 2**.



Scheme 3

Example	R1	R2,R5	N-Benzyl	HCl Salt
1	methyl	2-Ph	11	12
2	ethyl	2-OMe,5-F	13	14
3	ethyl	2-OCF3	15	16
4	ethyl	2-Ph	17	18
5	isopropyl	2-OMe, 5-F	19	20
6	isopropyl	2-OMe	21	22
7	isopropyl	2-Oet	23	24
8	isopropyl	2-OCF3	25	26
9	isopropyl	2-Ph	27	28
10	isopropyl	2-Ph,5-F	29	30
11	isobutyl	2-OMe, 5-F	31	32
12	isobutyl	2-Oet	33	34
13	isobutyl	2-OCF3	35	36
14	isobutyl	2-Ph	37	38
15	isobutyl	2-Ph, 5-F	39	40
16	cyclopentyl	2-OMe, 5-F	41	42
17	cyclopentyl	2-Oet	43	44
18	cyclopentyl	2-OCF3	45	46
19	cyclopentyl	2-Ph	47	48
20	cyclopentyl	2-Ph, 5-F	49	50
21	tetrahydropyranyl	2-OMe, 5-F	51	52
22	tetrahydropyranyl	2-OCF3	53	54
23	tetrahydropyranyl	2-Ph	55	56
24	tetrahydropyranyl	2-(3-F-Ph)	57	58
25	3,3,3-trifluoropropyl	2-OMe, 5-F	59	60
26	3,3,3-trifluoropropyl	2-OCF3	61	62
27	3,3,3-trifluoropropyl	2-Ph	63	64
28	4,4,4-trifluorobutyl	2-OMe, 5-F	65	66
29	4,4,4-trifluorobutyl	2-Ph	67	68
30	cyclopropyl	2-OMe	69	70
31	cyclopropyl	2-Oet	71	72
32	cyclopropyl	2-Ph	73	74

Table 2

Examples 1 to 32 can be otained in enantiomerically pure form *via* this route using chirally pure ester 1b. Resolution of 1 into 1a and 1b can be achieved through chiral HPLC. Addition of the benzyl Grignard reagent is a stereoselective process and gives predominantly one diastereomer with only small amounts of the second diastereomer. No epimerisation was observed during removal of the benzyl group. Alternatively, enantiomerically pure products are obtained through conversion to an N-protected analogue such as butyloxycarbonyl or carbobenzyloxy followed by separation by chiral

HPLC. Removal of the N-protecting group leads to enantiomerically highly enriched products.

In the experimental procedures described below the following abbreviations are used:

HPLC = high performance liquid chromatography

THF = tetrahydrofuran

DCM = dichloromethane

FIA^+ (or FIA-MS) = fast-ionisation-analysis mass spectrometry

LCMS = liquid chromatography mass spectroscopy

NMR = nuclear magnetic resonance

MW = molecular weight

MeOH = methanol

EtOAc or AcOEt = ethyl acetate

PS-DIEA = polymer-supported diisopropylethylamine

DEA = diethylamine

R_T = retention time

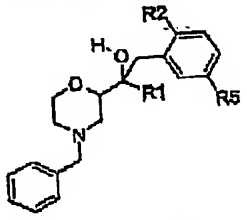
cbz = carbobenzyloxy

General Synthetic Procedures for the Preparation of Examples 1 to 32

***General Procedure 1*: Preparation of N-benzyl morpholine alkyl ketones**

To a solution of the carboxamide **2** or **2b** in anhydrous THF at 0°C is added a solution of the requisite Grignard reagent (1.2-3 eq in one or two aliquots). The reaction mixture is allowed to warm up to room temperature and left stirring for 45 minutes to 2 hours before quenching either with 1M hydrochloric acid or saturated ammonium chloride solution and extracting either in DCM or ethyl acetate. The combined organic layers are dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the corresponding alkyl ketones **3-10** and **77**.

***General Procedure 2*: Preparation of N-benzyl tertiary alcohols**



To a solution of the ketones **3-10** and **77** in anhydrous THF at 0°C is added a solution of the requisite benzyl Grignard reagent (1.1-1.5 eq). The reaction mixture is allowed to warm up to room temperature and left stirring for 1-2 hours before quenching by addition of cold water. After extraction of the aqueous layer in DCM, the combined organic layers are washed with brine, dried over magnesium sulphate, filtered and concentrated *in vacuo* to give the title N-benzyl tertiary alcohols. Purification details are listed for individual compounds.

***General Procedure 3*: Debenzylation of N-benzyl tertiary alcohols**

To a solution of the requisite N-benzyl tertiary alcohol in anhydrous DCM is added solid supported Hünig's base (Argonaut, 3.56 mmol/g, 2-4 eq) and α-chloroethyl chloroformate (3 to 10 eq) at room temperature under nitrogen. The reaction mixture is heated to 40°C and the reaction is monitored by FIA^+ and LCMS analysis. After completion the reaction mixture is filtered, and the resin washed with DCM. The combined organic phases are concentrated *in vacuo*. Methanol is added and the solution heated to 60°C for 1.5 to 8 hours. After complete consumption of starting material the methanol solution is evaporated to give a product, which is further purified as detailed for individual compounds.

***General Procedure 4*: Conversion of amines into hydrochloride salts**

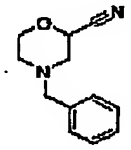
To a solution of the requisite amine in dry diethyl ether (5-10 ml) is added hydrochloric acid (1.2 eq, 1M solution in diethyl ether). Ether is blown off with a stream of nitrogen or removed *in vacuo* and the samples were either dried under high vacuum for several hours or freeze-dried (acetonitrile/water 1:1 [v/v]) to give the hydrochloride salts in near quantitative yield.

***General Procedure 5*: Preparation of benzyl Grignard reagents**

Such reagents were prepared from the requisite benzyl halide using methods known to those skilled in the art (see for example Fieser, L.F. and Fieser, M.F. "Reagents for Organic Synthesis", John Wiley and Sons Inc., Vol. 1, pp. 415-424 or March, J. "Advanced Organic Chemistry", John Wiley and Sons Inc., 3rd Ed., pp. 558-561). The requisite benzyl halides were either commercially available or prepared using previously published literature methods.

Preparation of Intermediates for the Synthesis of Examples 1-32

4-Benzyl-morpholine-2-carbonitrile

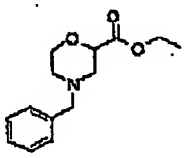


A one-litre reactor with mechanical stirring, cooled by an ice bath, is charged with *N*-benzylethanolamine (172.2 g; 1 equiv. available from Aldrich Chemical Company). 2-Chloroacrylonitrile (100 g; 1 equiv. available from Aldrich Chemical Company) is added dropwise over 2 minutes. The temperature is maintained between 23 °C and 29 °C by means of the ice bath and subsequently a water bath at 15 °C. After one night stirring at room temperature (water bath), the mixture is dissolved in tetrahydrofuran and transferred to a 2 L reactor which is cooled to –5 °C by ice/NaCl bath. The total volume of tetrahydrofuran is 1.35 L. Potassium *tert*-butoxide (148 g; 1.1 equiv.) is added by portions over 1 hour, keeping the reaction temperature at 0±2 °C. After 1 hour post-stirring at 0 °C, the mixture is quenched with saturated $NaHCO_3$ (500 mL). The aqueous layer is extracted with diethyl ether (500 mL). Organic layers are dried over $MgSO_4$ and evaporated to dryness. The title compound (149.8 g; 65%) is obtained after percolation of the 250 g dry residue on 1 kg of SiO_2, eluting with the following gradient:

5% AcOEt – 95% n-heptane	2.5 L
10% AcOEt – 90% n-heptane	2 L

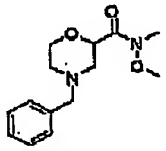
15% AcOEt – 85% n-heptane	2 L
20% AcOEt – 80% n-heptane	5 L

(R,S)-4-Benzyl-morpholine-2-carboxylic acid ethyl ester (1a,1b)



A stirred solution of 4-benzyl-morpholine-2-carbonitrile (113.0g, 0.56mole) in ethanol (1030ml) is treated with concentrated sulphuric acid (165ml) added in portions. (exothermic, internal temperature rises from ambient to 65 °C). The mixture is then warmed under reflux for 66hrs. The solution is cooled and then concentrated in vacuo to half volume, basified with aqueous potassium carbonate (beware frothing) and the product extracted into diethyl ether. The organic phase is dried over magnesium sulphate, filtered and evaporated to dryness in vacuo to yield an oil. This material is evacuated further under high vacuum. Yield = 121.3g (87%).

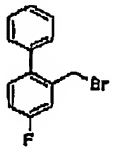
(R,S)-4-Benzyl-morpholine-2-carboxylic acid methoxy-methyl-amide (2a, 2b)



To a stirred suspension of *N,N*-dimethylhydroxylamine (6.6 g, 67.6 mmol) in anhydrous DCM (200 ml) under nitrogen at 0°C is added dropwise a solution of trimethylaluminium (2M solution in hexane, 34 ml, 67.6 mmol) over 30 minutes. The reaction mixture is allowed to warm up to room temperature and left stirring for 1 hour. A solution of the ester **1a, 1b** (6.74 g, 27 mmol) in anhydrous DCM (100 ml) is then added dropwise over 30 minutes and the reaction mixture left stirring overnight before quenching by cautious addition of phosphate buffer (disodium hydrogen phosphate, pH 8) solution. The precipitate is removed by filtration through a celite pad and the residue washed with chloroform. The organic phase is then concentrated *in vacuo* and washed with water. The aqueous layer is re-extracted with chloroform and the organic phases are combined, washed with brine, dried over magnesium sulphate and the solvent evaporated *in vacuo* to

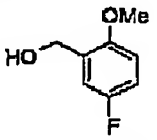
give **2a, 2b** as a yellow oil. Alternatively, the reaction could be worked up as follows: upon addition of a solution of the ester **1a, 1b** (1 eq) the reaction mixture is left stirring for 1 hour before quenching by addition of phosphate buffer (disodium hydrogen phosphate, pH 8) solution, followed by addition of water. The aqueous layer is re-extracted with DCM and the organic phases are combined, dried over magnesium sulphate and the DCM evaporated *in vacuo* to give **2a, 2b** as a yellow oil (3.36 g, 47 %). MW 264.33; $C_{14}H_{20}N_2O_3$; ^{1}H NMR ($CDCl_3$): 7.47-7.22 (5H, m), 4.55 (1H, d, 1.5 Hz), 4.00 (1H, dd, 11.5 Hz, 1.7 Hz), 3.75 (1H, dt, 11.5 Hz, 2.2 Hz), 3.65 (3H, s) 3.56 (2H, m), 3.17 (3H, s), 2.93 (1H, d, 11.3 Hz), 2.68 (1H, d, 11.3 Hz), 2.30 (2H, AB, 11.3 Hz); LCMS: (6 min method) m/z 265 $[M+H]^+$, Rt 0.65 min.

2-Phenyl-5-fluoro benzyl bromide



The title compound is prepared in 5 steps from commercially available (Aldrich) 5-fluorosalicylic acid following literature procedures (JACS, 2000, 122, 4020-4028). MW 265.13; $C_{13}H_{10}BrF$; ^{1}H NMR ($CDCl_3$): 7.48-7.38 (5H, m), 7.26-7.19 (1H, m), 7.05 (1H, td, 8.3 Hz, 2.8 Hz), 4.39 (2H, s); ^{19}F NMR ($CDCl_3$): -114.72.

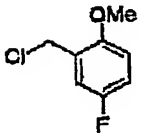
(5-Fluoro-2-methoxy-phenyl)-methanol



To a solution of 2-methoxy-5-fluorobenzaldehyde (11.093g, 1 equiv.- available from Aldrich Chemical Company) in methanol at -10 °C under nitrogen atmosphere is added $NaBH_4$ (7.515g, 2.7 equiv.) portionwise. The solution is allowed to warm to room temperature and after 30 minutes the reaction solvent is removed under reduced pressure and replaced with dichloromethane. This solution is poured onto ice water and further extracted with dichloromethane. The organic fractions are collected and dried ($MgSO_4$) and the solvent removed under reduced pressure to give the title compound as an oil (9.794g, 87%).^{1}H NMR (300MHz, $CDCl_3$): δ 2.58 (m, 1H), 3.81 (s, 3H), 4.63 (d, 2H, J =

6.3 Hz), 6.78 (dd, 1H, J = 8.9 and 4.3 Hz), 6.94 (td, 1H, J = 8.5 and 3.1Hz), 7.04 (dd, 1H, J = 8.7 and 3.1Hz).

5-fluoro-2-methoxybenzyl chloride

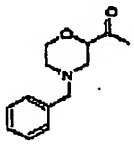


Neat (5-Fluoro-2-methoxy-phenyl)-methanol (19.587g, 1 equiv.) is added to neat $SOCl_2$ (42.2 mL, 4.6 equiv.) at –78°C under a nitrogen atmosphere and the solution is then allowed to warm to room temperature and stirred until evolution of gas ceases. An equivalent volume of anhydrous toluene is added to the flask and the solution heated to 60°C. On cooling, the reaction solution is poured onto ice water. The toluene layer is separated and dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude material is sublimed (60-80°C/0.05 mBarr) to give the title compound as a white solid (13.40 g, 61%). ^{1}H NMR (300MHz, $CDCl_3$): δ 3.87 (s, 3H), 4.60 (s, 2H), 6.79-7.20 (m, 3H).

2-methoxy-5-fluorobenzyl magnesium bromide

Magnesium turnings (21.6 g, 0.888 mole, 2 eq.) and diethyl ether (300 ml) are loaded in a reactor under N_2. A solution of 5-fluoro-2-methoxybenzyl chloride (116 g, 0.664 mole, 1.5 eq.) in diethyl ether (200 ml) is loaded in an addition funnel. Iodine crystals and a small amount of the 5-fluoro-2-methoxybenzyl chloride solution are added and the reaction mixture is stirred to initiate the reaction. The remainder of the 5-fluoro-2 methoxybenzyl chloride solution is then added drop-wise maintaining the temperature of the reaction mixture below 28 °C. The mixture is stirred for another 5 minutes at 19 °C and after completion of the addition and a white suspension is formed.

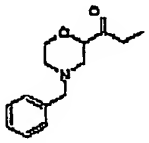
1-[4-(Phenylmethyl)morpholin-2-yl]ethan-1-one (3)



Compound **3** is obtained from **2b** (0.730 g, 2.8 mmol) and commercially available (Aldrich) methyl magnesium bromide (1.0M solution in THF, 3 ml, 3 mmol, 1.1 eq) in

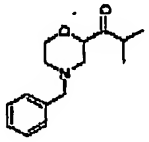
anhydrous THF (25 ml) following *General Procedure 1* after purification by automated column chromatography (EtOAc/n-heptane 14-100% gradient) (0.3 g, 49%). MW 235.33; $C_{14}H_{21}NO_2$. LCMS (6 minute method) m/z 220.1 $[M+H]^+$, R_T 1.55 min.

1-[4-(Phenylmethyl)morpholin-2-yl]propan-1-one (4)



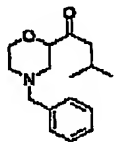
Compound **4** is obtained from **2b** (0.70 g, 2.65 mmol) and commercially available (Aldrich) ethyl magnesium bromide (2.65 ml, 7.94 mmol, 3 eq) in anhydrous THF (25 ml) following *General Procedure 1* as a yellow oil (583 mg, 89%). MW 249.36; $C_{15}H_{23}NO_2$.

2-Methyl-1-[4-(phenylmethyl)morpholin-2-yl]propan-1-one (5)



Compound **5** is obtained from **2b** (3.018 g, 11.4 mmol) and commercially available (Aldrich) isopropyl magnesium chloride (2M/THF, 17.1 ml, 34.3 mmol, 3 eq) in THF (100 ml), following *General Procedure 1* as a yellow oil (2.68 g, 89%); MW 263.38; $C_{16}H_{25}NO_2$); LCMS (6 minute method): m/z 248.2 $[M+H]^+$, R_T 2.41min.

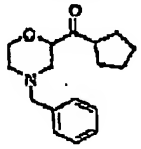
3-Methyl-1-[4-(phenylmethyl)morpholin-2-yl]butan-1-one (6)



Compound **6** is prepared from **2** (10 g, 37 mmol) in anhydrous tetrahydrofuran (50 ml) and commercially available (Aldrich) isobutyl magnesium bromide (2M solution in diethyl ether, 56 mmol, 28 ml, 1.5 eq) following *General Procedure 1*. After stirring for 1 hour the reaction is quenched by addition of aqueous hydrochloric acid (150 ml). THF is removed in vacuo and diethyl ether is added after pH adjustment by addition of a saturated sodium bicarbonate solution. The organic phases are combined, dried over

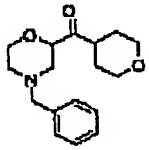
magnesium sulphate and the solvent is removed *in vacuo*. **6** is isolated in 80% purity (8.7 g, 67 % with respect to pure product). MW 261.37; $C_{16}H_{23}NO_2$; LCMS: (6 min method) m/z 262.2 $[M+H]^+$, R_T 2.753 min.

Cyclopentyl[4-(phenylmethyl)morpholin-2-yl]methanone (7)



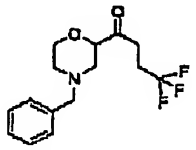
Compound **7** is prepared from **2** (3.36 g, 12.7 mmol) in anhydrous tetrahydrofuran (120 ml) and commercially available (Aldrich) cyclopentyl magnesium bromide (2M solution in diethyl ether, 19.1 ml, 38.2 mmol, 3 eq following *General Procedure* 1 in quantitative yield as yellow oil. MW 273.38; $C_{17}H_{23}NO_2$; LCMS: (6 min method) m/z 274 $[M+H]^+$, R_T 2.24 min.

[4-(Phenylmethyl)morpholin-2-yl][tetrahydro-2H-pyran-4-yl]methanone (8)



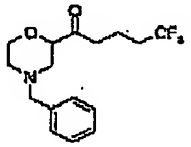
Compound **8** is obtained from **2b** (2.84 g, 10.74 mmol) in anhydrous tetrahydrofuran (30 ml) and 4-tetrahydropyranyl magnesium chloride (Chem. Ber. 98,1965, 3757) (2M solution in tetrahydrofuran, 6.5 ml, 13 mmol, 1.2 eq) following *General Procedure 1*. After 30 minutes further 4-tetrahydropyranyl magnesium chloride is added (2M solution in diethyl ether, 6.5 ml, 13 mmol, 1 eq.). After stirring for 2 hours the reaction mixture is quenched by addition of ammonium chloride solution (30 ml) and ethyl acetate (30 ml). The aqueous layer is re-extracted with ethylacetate (30 ml) and the organic phases are combined, dried over magnesium sulphate and the solvents are removed *in vacuo*. The resulting residue is purified by ion exchange ion exchange chromatography to give **8** as a yellow oil (2.98 g, 96 %). MW 289.38; $C_{17}H_{23}NO_3$. LCMS: (6 min method) m/z 290 $[M+H]^+$, R_T 2.20 min.

5,5,5-Trifluoro-1-[4-(phenylmethyl)morpholin-2-yl]butan-1-one (9)



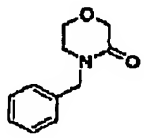
Compound **9** is obtained from **2b** (1.38g, 5.23mmol) and 3,3,3-trifluoropropyl magnesium bromide (20.9mls, 10.50mmol, 2eq) in dry THF (45ml) following *General procedure 1*. 3,3,3-Trifluoropropyl magnesium bromide is obtained from commercially available (Aldrich) 3,3,3-trifluoropropyl bromide following *General Procedure 5*. Purification by ion exchange chromatography gives **9** as oil (1.24g, 78.7%). MW 301.31; $C_{15}H_{18}F_3NO_2$. LCMS (6 minute method): m/z 302.4 $[M+H]^+$, R_T 2.66min.

5,5,5-Trifluoro-1-[4-(phenylmethyl)morpholin-2-yl]pentan-1-one (10)



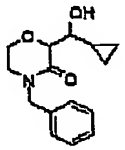
Compound **10** is prepared from a solution of **2** (0.717 g, 2.71 mmol) in anhydrous tetrahydrofuran (20 ml) and 4,4,4-trifluorobutyl magnesium bromide (0.5M solution in diethyl ether, 6.5 ml, 3.25 mmol, 1.2eq). 4,4,4-Trifluorobutyl magnesium bromide is obtained from commercially available (Aldrich) 4,4,4-trifluorobutyl bromide following *General Procedure 5*. After 30 minutes another 0.3 eq of 4,4,4-trifluorobutyl magnesium bromide are added (0.5M solution in diethyl ether, 2.5 ml). After stirring for 2 hours the solvents are removed *in vacuo* and water (20 ml) and ethyl acetate (30 ml) are added to the residue. The organic phase is washed with brine, dried over magnesium sulphate and the solvent is removed *in vacuo* to give **10** as clear oil (0.985 g). **10** is taken onto the next step without further purification. MW 315.34; $C_{16}H_{20}NO_2F_3$; LCMS: (6 min method) m/z 316 $[M+H]^+$, R_T 2.9min.

4-Benzylmorpholin-3-one



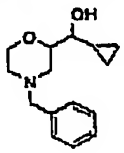
A solution of *N*-benzyl-*N*-(2-hydroxyethyl) chloroacetamide (627.7 g, 2.76 mol) in *tert*-butanol (0.9 l) is stirred under nitrogen while warming to 25-30°C. Potassium tert-butoxide (2.897 l of a 1M solution in *tert*-butanol, 2.90 mol, 1.05 eq) is added over 2 hours. The reaction mixture is then stirred at room temperature for 90 minutes. Ice-cold water (6 l) is added and the resultant cloudy solution extracted with ethyl acetate. The combined organic layers are washed with brine, dried over magnesium sulphate and evaporated *in vacuo* to give a light brown oil (441 g, 84%), which is used in the next stage without further purification; MW 191.23; $C_{11}H_{13}NO_2$; ^{1}H NMR ($CDCl_3$): 7.29-7.40 (5H, m), 4.67 (2H, s), 4.28 (2H, s), 3.87 (2H, t, 5 Hz), 3.31 (2H, t, 5 Hz); LCMS: (12 min method) m/z 192 $[M+H]+$ @ Rt 1.00 min.

4-Benzyl-2-(cyclopropyl-hydroxy-methyl)-morpholin-3-one (75)



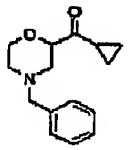
To a solution of 4-benzyl-morpholin-3-one (9.5 g, 50 mmol) in THF (200 ml) is added lithium diisopropylamide (2M solution in THF, 27 ml, 54 mmol, 1.1 eq) dropwise over 20 minutes at -78°C followed by slow addition of cyclopropyl methylaldehyde (3.85 ml, 55 mmol, 1.1 eq). After stirring at -78°C for one hour the reaction mixture is allowed to warm to room temperature and stirred for another 6 hours. The reaction is quenched by addition of EtOAc and brine. The aqueous layer is extracted with EtOAc, the combined organic layers are dried over magnesium sulphate and reduced *in vacuo*. Purification using automated column chromatography (DCM/MeOH, 0 to 15% gradient) gives 75 in 70% purity with 4-benzyl-morpholin-3-one as the major impurity. This product is directly used in the next step. MW 261.32; $C_{15}H_{19}NO_3$; ^{1}H NMR ($CDCl_3$): LCMS: (6 min method) m/z 261.32 $[M+H]^+$, R_T 2.23

(4-Benzyl-morpholin-2-yl)-cyclopropyl-methanol (76)



Borane-THF complex (1M solution in THF, 30 ml, 30 mmol, 4.1 eq) is added slowly to a solution of 75 (1.9 g, 7.3 mmol) in THF (100 ml). The reaction is heated to 60°C. After 24 hours MeOH and hydrochloric acid (2M, excess) are added and the resulting mixture heated for one hour at the same temperature. After careful addition of saturated $NaHCO_3$ solution and EtOAc the aqueous layer is extracted with EtOAc. The combined organic layers are washed with, brine, dried over magnesium sulphate and the solvent is removed *in vacuo*. Purification by ion exchange chromatography gives 76 (1.1 g, 61%). MW 247.34; $C_{15}H_{21}NO_2$; ^1H NMR ($CDCl_3$): LCMS: (6 min method) m/z 0.64 $[M+H]^+$, R_T 2.48 min.

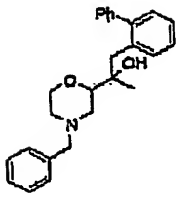
Cyclopropyl[4-(phenylmethyl)morpholin-2-yl]methanone (77)



A solution of dimethylsulphoxide (0.69 ml, 9.7 mmol, 2.2 eq) in DCM (4.5 ml) is slowly added to a solution of oxalyl chloride (2.43 ml, 4.85 mmol, 1.1 eq) in DCM (2.5 ml) followed by a solution of 76 (1.09 g, 4.41 mmol) in DCM (0.7 ml) under nitrogen at –60°C. After stirring for 15 minutes, triethylamine (3.14 ml, 22.1 mmol, 5 eq) is added and stirring continues for 15 minutes. After addition of water, the layers are separated. The aqueous layer is washed with DCM. The combined organic layers are washed with brine, dried over magnesium sulphate and the solvent is removed *in vacuo*. Purification using automated column chromatography (EtOAc/n-hexane, 20-50% gradient) gives 77 as a yellow oil (0.69 g, 64%). MW 245.32; $C_{15}H_{19}NO_2$; ^1H NMR ($CDCl_3$): LCMS: (6 min method) m/z 246.3 $[M+H]^+$, RT 1.095min.

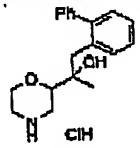
Example 1: Preparation of 1-[1,1'-biphenyl]-2-yl-2-morpholin-2-ylpropan-2-ol hydrochloride (12)

1-[1,1'-Biphenyl]-2-yl-2-[4-(phenylmethyl)mopholin-2-ylpropan-2-ol (11)



Compound **11** is prepared from 2-phenylbenzyl magnesium bromide (0.25M solution in diethyl ether, 5.5 ml, 1.38 mmol) and **3** (275 mg, 1.25 mmol) in anhydrous THF (7 ml) following *General Procedure 2*). 2-Phenylbenzyl magnesium bromide is obtained from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Further equivalents of 2-phenylbenzyl magnesium bromide (10 ml, 2.5 mmol) are added before quenching the reaction with ice water (7 ml). **11** is obtained as an oil in 75% purity after ion exchange (5 g column) chromatography and automated column chromatography (0-50% EtOAc/heptane gradient) and taken onto the next step without further purification (0.23 mg isolated material). MW 387.53; $C_{26}H_{29}NO_2$. LCMS (6 minute method): m/z 388.2 $[M+H]^+$, R_T 3.37 min.

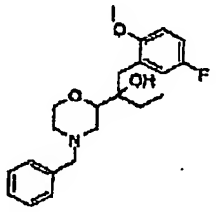
1-[1,1'-Biphenyl]-2-yl-2-morpholin-2-ylpropan-2-ol hydrochloride (12)



12 is obtained from **11** (204 mg, 0.53 mmol), α–chloroethyl chloroformate (0.23 ml, 2.11 mmol) and polymer-supported Hünig's base (296 mg, 1.05 mmol) in DCM (5 ml) following *General Procedure 3*, Purification using ion exchange chromatography, followed by preparative LCMS and conversion into the hydrochloride salt following *General Procedure 4* gives **12** as a foam (102 mg, 65%). MW 297.36; $C_{19}H_{23}NO_2$. HCl; ^{1}H NMR (CD_3OD) δ_H 7.15-7.39 (8H, m), 7.07-7.11 (1H, m), 3.97 (1H, dd, 3.0 Hz, 13.0 Hz), 3.56-3.65 (1H, m), 3.20-3.25 (1H, m), 3.08 (2H, t, 12.5 Hz), 2.82-2.99 (4H, m), 0.60 (3H, s). LCMS (12 minute method): m/z 298.2 $[M+H]^+$, R_T 4.38 min.

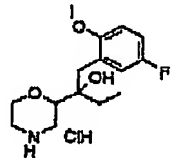
Example 2: Preparation of 1-[5-fluoro-2-(methyloxy)phenyl]-2-morpholin-2-ylbutan-2-ol hydrochloride (14)

1-[5-Fluoro-2-(methyloxy)phenyl]-2-[4-(phenylmethyl)morpholin-2-yl]butan-2-ol (13)



Compound 13 is obtained from 4 (583 mg, 2.5 mmol) and 2-methoxy-5-fluorobenzyl magnesium bromide (5.5 ml, 2.75 mmol, 1.1eq) in anhydrous THF (15 ml) following *General Procedure 2*. Further equivalents of 2-methoxy-5-fluorobenzyl magnesium bromide (2M solution in diethyl ether, 10 ml, 5.0 mmol) are added after 30 min and the mixture is warmed to room temperature and left to stir over night. After purification by ion exchange chromatography **13** is obtained as a yellow oil in 67% purity (702 mg). The compound is taken over to the next step without further purification. MW 373.47, $C_{22}H_{28}FNO_3$. LCMS (6 minute method) m/z 374.2 $[M+H]^+$, R_T 3.17 min.

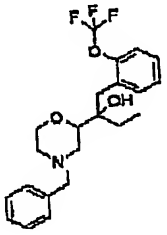
1-[5-Fluoro-2-(methyloxy)phenyl]-2-morpholin-2-ylbutan-2-ol hydrochloride (14)



14 is obtained from **13** (717 mg, 1.92 mmol), α–chloroethyl chloroformate (0.83 ml, 3.84 mmol, 4eq) and polymer-supported Hünig's base (1.08 g, 3.84 mmol, 2eq) in DCM (17 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by preparative LCMS and conversion into the hydrochloride salt following *General Procedure 4* gives **14** as a solid (185 mg, 30%). MW 319.81; $C_{15}H_{22}FNO_3$.HCl. ^1H NMR (CD_3OD) δ_H 6.94 (1H, dt, 1.5 Hz, 9 Hz), 6.81-6.84 (2H, m), 4.07 (1H, dd, 3.5, 13 Hz), 3.67-3.76 (4H, m), 3.56 (1H, dd, 2.5 Hz, 11 Hz), 3.33 (1H, m), 3.14-3.25 (1H, m), 3.00-3.08 (2H, m), 2.84 (2H, AB, 14 Hz), 1.37-1.51 (1H, m), 1.05-1.19 (1H, m), 0.82 (3H, t, 7.5 Hz). LCMS (12 minute method): m/z 284.1 $[M-HCl+H]^+$, R_T 3.76 min.

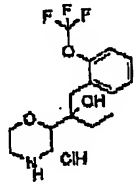
Example 3: Preparation of 2-morpholin-2-yl-1-{2-[(trifluoromethyl)oxy] phenyl}butan-2-ol hydrochloride (16)

2-[4-(Phenylmethyl)morpholin-2-yl]-1-{2-[trifluoromethyl)oxy]phenyl}butan-2-ol (15)



Compound 15 is obtained from 4 (1.1 mg, 4.71 mmol) and commercially available (Fluorochem) 2-trifluoromethoxy benzyl magnesium bromide (10.4 ml, 5.19 mmol, 1.1eq) in anhydrous THF (31 ml) following *General Procedure 2*. After 30 minutes further equivalents of 2-trifluoromethoxy benzyl magnesium bromide are added (0.5M solution in diethyl ether, 4.71 ml, 2.36 mmol). Purification by ion exchange chromatography gives 15 as an oil (1.88 g, 98%). MW 409.45; $C_{22}H_{26}F_3NO_3$. LCMS (6 minute method): m/z 410.4 $[M+H]^+$, R_T 3.28 min.

2-Morpholin-2-yl-1-{2-[(trifluoromethyl)oxy]phenyl}butan-2-ol hydrochloride (16)

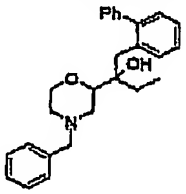


16 is obtained from 15 (1.88 g, 4.59 mmol), α–chloroethyl chloroformate (1.98 ml, 18.4 mmol) and polymer-supported Hünig's base (2.58 g, 9.18 mmol) in DCM (40 ml) following *General Procedure 3*. Purification using ion exchange chromatography followed by automated column chromatography (0-20% MeOH/DCM gradient) and conversion to the hydrochloride salt following *General Procedure 4* gives 16 (258.5 mg, 17%) as a white solid. MW 319.33, $C_{15}H_{20}F_3NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.53 (1H, dd, 2 Hz, 7.5 Hz), 7.27-7.38 (3H, m), 4.20 (1H, dd, 3.5 Hz, 13 Hz), 3.85 (1H, td, 3 Hz, 13 Hz), 3.70 (1H, dd, 2 Hz, 11 Hz), 3.44 (1H, d, 13 Hz), 3.27-3.34 (1H, m), 3.12-3.22 (2H, m), 3.07 (1H, d, 14 Hz), 2.96 (1H, d, 14 Hz), 1.55 (1H, sextet, 7.5 Hz), 1.26 (1H, sextet,

7.5 Hz), 0.93 (3H, t, 7.5 Hz). LCMS (12 minute method): m/z 320.4 $[M+H]^+$, R_T 2.77 min.

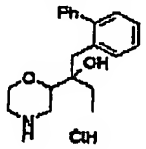
Example 4: Preparation of 1-[1,1'-biphenyl]-2-yl-2-morpholin-2-ylbutan-2-ol hydrochloride (18)

1-[1,1'-Biphenyl]-2-yl-2-[4-(phenylmethyl)morpholin-2-ylbutan-2-ol (17)



Compound **17** is obtained from **3** (601 mg, 2.58 mmol) and 2-phenylbenzyl magnesium bromide (0.25M solution in diethyl ether, 11.5 ml, 2.84 mmol) in anhydrous THF (15 ml) following *General Procedure 2*. 2-Phenylbenzyl magnesium bromide is prepared from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Further equivalents of 2-phenylbenzyl magnesium bromide (10.32 ml, 2.58 mmol) are added. Purification by ion exchange chromatography followed by automated column chromatography (0-50% EtOAc/n-heptane, gradient) gives **17** (705 mg, 68%) as a colourless oil in 91% purity which is directly used in the next step. MW 401.55, $C_{27}H_{31}NO_2$. LCMS (6 minute method): m/z 402.2 $[M+H]^+$, R_T 3.56 min

1-[1,1'-Biphenyl]-2-yl-2-morpholin-2-ylbutan-2-ol hydrochloride (18)

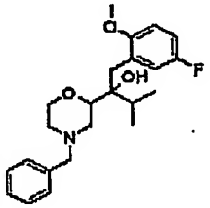


18 is obtained from **17** (705 mg, 1.76 mmol), α-chloroethyl chloroformate (0.76 ml, 7.02 mmol) and polymer-supported Hünig's base (988 g, 3.52 mmol) in DCM (15 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by automated column chromatography (5-20% MeOH/DCM gradient) and conversion into the hydrochloride salt following *General Procedure 4* gives **18** (0.37 g, 62%) as a yellow foam. MW 347.82, $C_{20}H_{25}NO_2.HCl$ ^1H NMR (CD_3OD) δ_H 7.43-7.46 (1H, m), 7.29-7.34 (3H, m), 7.14-7.25 (5H, m), 7.06-7.11 (1H, m), 3.94 (1H, dd, 3.5 Hz, 13 Hz),

3.55-3.64 (1H, m), 3.37 (1H, dd, 1.5 Hz, 11 Hz), 3.09 (2H, d, 12.5 Hz), 2.80-2.99 (4H, m), 1.11-1.23 (1H, m), 0.91 (1H, m), 0.38 (3H, t, 7.5 Hz). LCMS (12 minute method): m/z 312.1 $[M+H]^+$, R_T 4.67 min.

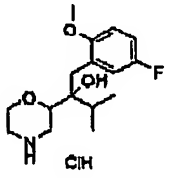
Example 5: Preparation of 1-[5-fluoro-2-(methyloxy)phenyl]-3-methyl-2-morpholin-2-ylbutan-2-ol hydrochloride (20)

1-[5-Fluoro-2-(methyloxy)phenyl]-3-methyl-2-[4-(phenylmethyl)morpholin-2-yl]butan-2-ol (19)



Compound **19** is obtained from **5** (0.7 g, 2.83 mmol) and 2-methoxy-5-fluoro-benzyl magnesium bromide (6.2 ml, 3.11 mmol, 1.1eq) in anhydrous THF (15 ml) following *General Procedure 2*. Further equivalents of 2-methoxy-5-fluoro-benzyl magnesium bromide (8.49 ml, 4.25 mmol) are added and mixture is warmed to room temperature and left to stir over night. Purification using automated column chromatography (0-25% n-heptane/EtOAc gradient) gives **19** (0.53 g, 48%). MW 387.5; $C_{23}H_{30}FNO_3$. LCMS (6 minute method): m/z 388.2 $[M+H]^+$, R_T 3.21 min.

1-[5-fluoro-2-(methyloxy)phenyl]-3-methyl-2-morpholin-2-ylbutan-2- hydrochloride (20)

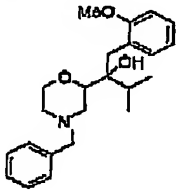


20 is obtained from **19** (523 mg, 1.35 mmol), α–chloroethyl chloroformate (0.58 ml, 5.40 mmol, 4eq) and PS-DIEA (0.76 g, 2.70 mmol, 2eq) in DCM (10 ml) following *General Procedure 4*. Purification by ion exchange chromatography and conversion to the hydrochloride salt following *General Procedure 4* gives **20** as an off-white solid (0.26g,

58%). MW 333.83, $C_{16}H_{24}FNO_3$. HCl. ^1H NMR (CD_3OD) δ_H 7.10 (1H, d, 9.5 Hz), 6.94 (2H, d, 6 Hz), 4.07 (1H, dd, 3.5 Hz, 13 Hz), 3.71-3.88 (5H, m), 3.21-3.47 (2H, m), 2.99-3.11 (4H, m), 1.8 (1H, septet, 7 Hz), 1.04 (3H, d, 7 Hz), 0.94 (3H, d, 7.0 Hz). LCMS (12 minute method): m/z 298 $[M\text{-}HCl+H]^+$, R_T 4.29 min.

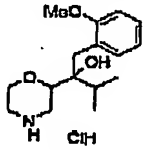
Example 6: Preparation of 3-methyl-1-[2-methyloxy)phenyl]-2-morpholin-2-ylbutan-2-ol hydrochloride (22a, 22b)

2-(4-Benzyl-morpholin-2-yl)-1-(2-methoxy-phenyl)-3-methyl-butan-2-ol (21)



Compound **21** is obtained from **5** (1.5 g, 6.06 mmol) and 2-methoxy benzyl magnesium bromide (available from Rieke-Metals) (0.25M solution in THF, 33.9 ml, 8.49 mmol) in anhydrous THF (30 ml) following *General Procedure 1*. Purification by column chromatography (0-40% EtOAc/n-heptane gradient) gives **21** as colourless oil (1.45 g, 84%). MW 369.51, $C_{23}H_{31}NO_3$.HCl. LCMS (6 minute method): m/z 370.2 $[M+H]^+$, R_T 2.77 min.

3-Methyl-1-[2-methyloxy)phenyl]-2-morpholin-2-ylbutan-2-ol hydrochloride (22a, 22b)

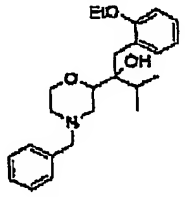


22a,22b is obtained from **21** (1.24 mg, 3.37 mmol), α–chloroethyl chloroformate (3.63 ml, 33.7 mmol) and polymer-supported Hünig's base (4.72 g, 16.8 mmol) in DCM (45 ml) following *General Procedure 3*. Purification using ion exchange chromatography followed by chiral preparative HPLC (Heptane:EtOH:DEA 85:15:0.2 gradient, chiralcel-OD) gives the first eluting enantiomer **22a** (RT 9.5min), and the second eluting enantiomer **22b** (RT 11.41min). The two enantiomers are converted to their respective hydrochloride salt **22a** (146 mg) and **22b** (138 mg) and obtained as white solids (28%

overall combined yield). MW 315.84; $C_{16}H_{25}NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.22-7.34 (2H, m), 6.85-6.95 (2H, m), 4.08 (1H, dd, 3.6 12.8 Hz), 3.86-3.9 (4H, m), 3.77 (1H, td, 2.45 Hz, 12.4 Hz), 3.22-3.28 (1H, m), 3.24 (1H, d, 12.8 Hz), 2.95-3.11 (4H, m), 1.83 (1H, septet, 6.8 Hz), 1.16 (3H, d, 7.0 Hz), 0.95 (3H, d, 7.0 Hz). LCMS (12 minute method): m/z 280.2 $[M-HCl+H]^+$, R_T 4.05 min.

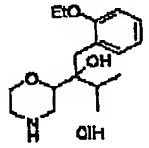
Example 7: Preparation of 1-[2-ethyloxy)phenyl]-3-methyl-2-morpholin-2-ylbutan-2-ol hydrochloride (24a, 24b)

1-[2-Ethyloxy)phenyl]-3-methyl-2-[4-phenylmethyl)morpholin-2-ylbutan-2-ol (23)



Compound **23** is obtained from **5** (1.5 g, 6.06 mmol) and 2-ethoxybenzyl magnesium chloride (available from Rieke-Metals) (0.25M solution in THF, 34 ml, 8.49 mmol) in anhydrous THF (30 ml) following *General Procedure 2*. After repeated purification by column chromatography (100% DCM to 10% MeOH/ DCM gradient followed by 100% DCM to 1:1 EtOAc: DCM gradient) **23** is obtained as colourless oil (0.8 g, 35%). MW 383.54, $C_{24}H_{33}NO_3$. LCMS (6 minute method): m/z 384.4 $[M+H]^+$, R_T 3.04 min.

1-[2-Ethyloxy)phenyl]-3-methyl-2-morpholin-2-ylbutan-2-ol hydrochloride (24a, 24b)

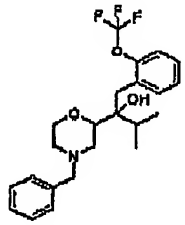


24a, 24b are obtained from **23** (766 mg, 2.0 mmol), α–chloroethyl chloroformate (0.86 ml, 8.0 mmol) and polymer-supported Hünig's base (1.12 g, 4.0 mmol) in DCM (30 ml) following *General Procedure 3*. Purification using ion exchange chromatography followed by automated column chromatography (0-20% MeOH/ DCM gradient) and chiral preparative chromatography (Heptane:EtOH:DEA 95:5:0.2 gradient, chiracel AD) gives the first eluting enantiomer, R_T 13.40min, and the second eluting enantiomer, R_T 15.63min. After conversion to their respective hydrochloride salt **24a** (85 mg) and **24b**

(79 mg) are obtained as brown solids (28% combined yield). MW 293.36; $C_{17}H_{27}NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.06-7.09 (1H, m), 6.95-7.01 (1H, m), 6.66-6.75 (2H, m), 3.80-3.92 (3H, m), 3.46-3.63 (2H, m), 2.96-3.15 (2H, m), 2.66-2.86 (4H, m), 1.54-1.63 (1H, m), 1.22 (3H, t, 7.0 Hz), 0.82 (3H, d, 7.0 Hz), 0.71 (3H, d, 7.0 Hz). LCMS (12 minute method): m/z 294.2 $[M+H]^+$, R_T 4.60 min.

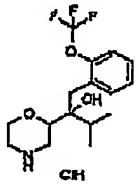
Example 8: 3-Methyl-2-morpholin-2-yl-1-{2-[(trifluoromethyl)oxy]butan-2-ol hydrochloride (26)

3-Methyl-2-[4-(phenylmethyl)morpholin-2-yl]-1-{2-[(trifluoromethyl)oxy] phenyl}butan-2-ol (25)



Compound **25** is obtained from **5** (953 mg, 3.85 mmol) and commercially available (Fluorochem) 2-trifluoromethoxy benzyl magnesium bromide (8.48 ml, 4.24 mmol, 1.1eq) in anhydrous THF (25 ml) following *General Procedure 3* and addition of further 2-trifluoromethoxy benzyl magnesium bromide (3.85 ml, 1.93 mmol). Purification by ion exchange chromatography gives **25** as a yellow oil in 86% purity which is used in the next step without further purification (1.53 g of isolated material). MW 423.38; $C_{23}H_{28}F_3NO_3$. LCMS (6 minute method) m/z 424.1 $[M+H]^+$, R_T 3.53min.

3-Methyl-2-morpholin-2-yl-1-{2-[(trifluoromethyl)oxy]butan-2-ol hydrochloride (26)

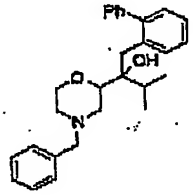


26 is obtained from **25** (1.53 g, 3.61 mmol), α-chloroethyl chloroformate (1.55 ml, 14.5 mmol, 4eq) and polymer-supported Hünig's base (2.03 g, 7.23 mmol, 2eq) in DCM (30 ml) following *General Procedure 3*. Purification by ion exchange chromatography,

followed by automated column chromatography (0-20% MeOH/DCM gradient) and conversion to its hydrochloride salt following *General Procedure 4* gives **26** as a yellow solid (0.4 g, 29%). MW 379.82; $C_{16}H_{22}F_3NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.46 (1H, dd, 1.5 Hz, 7.5 Hz), 7.14-7.24 (3H, m), 3.94 (1H, dd, 3.5 Hz, 13 Hz), 3.80 (1H, dd, 2.5 Hz, 11.5 Hz) 3.69 (1H, td, 2.5 Hz, 13 Hz), 3.27 (1H, d, 13 Hz), 3.13 (1H, d, 12.5 Hz), 2.72-3.02 (4H, m), 1.70 (1H, septet, 7 Hz), 0.94 (3H, d, 7 Hz), 0.84 (3H, d, 7.0 Hz). LCMS (12 minute method): m/z 334.4 $[M+H]^+$, R_T 2.94 min.

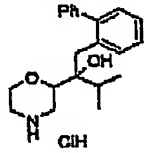
Example 9: Preparation of 1-[1,1'-biphenyl]-2-yl-3-methyl-2-morpholin-2-ylbutan-2-ol hydrochloride (28)

1-[1,1'-Biphenyl]-2-yl-3-methyl-2-[4-(phenylmethyl)morpholin-2-ylbutan-2-ol (27)



Compound **27** is obtained from **5** (0.7 g, 2.83 mmol) and 2-phenylbenzyl magnesium bromide (12.5 ml, 3.11 mmol) in anhydrous THF (15 ml) following *General Procedure 2* and further equivalents of 2-phenylbenzyl magnesium bromide reagent (11.3 ml, 5.66 mmol). 2-Phenylbenzyl magnesium bromide is prepared from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Purification using ion exchange chromatography, followed by automated column chromatography (0-20% EtOAc/n-heptane gradient) gives **27** as oil (0.46 g, 40%). MW 415.58; $C_{28}H_{33}NO2$. LCMS (6 minute method): m/z 416.2 $[M+H]^+$, R_T 3.45min.

1-[1,1'-Biphenyl]-2-yl-3-methyl-2-morpholin-2-ylbutan-2-ol hydrochloride (28)

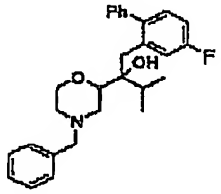


28 is obtained from **27** (405 mg, 0.976 mmol), α–chloroethyl chloroformate (0.42 ml, 3.9 mmol) and polymer-supported Hünig's base (0.55 g, 1.95 mmol) in DCM (7 ml)

following *General Procedure 3*. The crude product is purified using ion exchange chromatography, and then converted to its hydrochloride salt following *General Procedure 4* to give **28** as a white solid (0.23 g, 71%). MW 361.91; $C_{21}H_{27}NO_2$.HCl. ^1H NMR (CD_3OD) δ_H 7.61-7.64 (1H, m), 7.19-7.47 (8H, m), 3.95 (1H, dd, 4 Hz, 13 Hz), 3.61-3.71 (2H, m), 3.04- 3.19 (4H, m), 2.96 (1H, td, 4 Hz, 12.6 Hz), 2.70 (1H, dd, 13, 11.5 Hz), 1.67 (1H, septet, 7 Hz), 0.75 (3H, d, 7 Hz), 0.63 (3H, d, 7 Hz). LCMS (12 minute method): m/z 326.2 $[M+H]^+$, R_T 5.02 min.

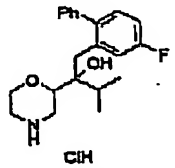
Example 10: Preparation of 1-(4-Fluoro[1,1'-biphenyl]-2-yl)-3-methyl-2-morpholin-2-ylbutan-2-ol hydrochloride (30)

1-(4-Fluoro[1,1'-biphenyl]-2-yl)-3-methyl-2-[4-(phenylmethyl)morpholin-2-ylbutan-2-ol hydrochloride (29)



Compound **29** is obtained from **5** (1.13 g, 4.57 mmol) and 2-phenyl-5-fluorobenzyl magnesium bromide (0.5M in THF, 10.5 ml, 5.03 mmol) in anhydrous THF (30 ml) following *General Procedure 2* (further 2-phenyl-5-fluorobenzyl magnesium bromide (0.33eq, 3 ml, 1.51 mmol) is added after 30 min). 2-Phenyl-5-fluorobenzyl magnesium bromide is obtained from 2-phenyl-5-fluorobenzyl bromide following *General Procedure 5*. Purification by ion exchange chromatography followed by automated column chromatography (0-20% EtOAc/n-heptane gradient) gives **29** as a yellow oil in 86% purity which is directly used in the next step (1.58 g recovered material). MW 415.58; $C_{28}H_{33}NO_2$. LCMS (6 minute method): m/z 434.5 $[M+H]^+$, R_T 3.71 min

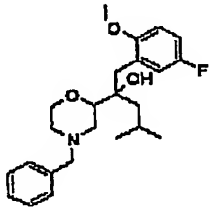
1-(4-Fluoro[1,1'-biphenyl]-2-yl)-3-methyl-2-morpholin-2-ylbutan-2-ol hydrochloride (30)



30 is obtained from **29** (1.58 g, 3.63 mmol), α–chloroethyl chloroformate (1.57 ml, 3.63 mmol) and polymer-supported Hünig's base (2.04 g, 7.26 mmol) in DCM (30 ml) following *General Procedure 3*. The crude product is purified using ion exchange chromatography, automated column chromatography (0-20% MeOH/ DCM gradient, 40 g column), and preparative LCMS. Conversion to the hydrochloride salt following *General Procedure 4* gives **30** as a yellow solid (0.3 g, 22%). MW 379.91; $C_{21}H_{26}FNO_2.HCl$. ^1H NMR (CD_3OD) δ_H 7.20-7.35 (6H, m), 7.07-7.14 (1H, m), 6.90 (1H, td, 2.5 Hz, 8.5 Hz), 3.83 (1H, d, br, 10 Hz), 3.56 (2H, t, 10 Hz), 3.03-3.12 (2H, m), 2.79-2.98 (3H, m), 2.63 (1H, t, 11.5 Hz), 1.55 (1H, quintet, 7 Hz), 0.64 (3H, d, 7 Hz), 0.51 (3H, d, 7 Hz). LCMS (12 minute method): m/z 344.1 $[M-HCl+H]^+$, R_T 5.14 min.

Example 11: Preparation of 1-[5-fluoro-2-(methyloxy)phenyl]-4-methyl-2-morpholin-2-yl-pentan-2-ol hydrochloride (32)

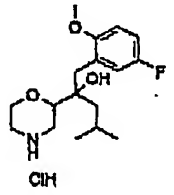
1-[5-Fluoro-2-(methyloxy)phenyl]-4-methyl-2-[4-(phenylmethyl)morpholin-2-yl]pentan-2-ol (31)



Compound **31** is obtained from **6** (465 mg, 1.78 mmol) and 2-methoxy-5-fluorobenzyl magnesium bromide (3.92 ml, 1.96 mmol, 1.1eq) in dry THF (10 ml) following *General Procedure 2*. Purification by ion exchange chromatography followed by automated column chromatography (0-40% EtOAc/n-heptane gradient) gives **31** as an oil (448 mg,

83% purity). MW 401.53; $C_{24}H_{32}FNO_3$. LCMS (6 minute method): m/z 402.2 $[M+H]^+$, R_T 3.40 min.

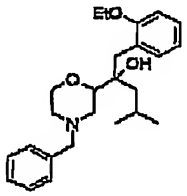
1-[5-Fluoro-2-(methyloxy)phenyl]-4-methyl-2-morpholin-2-ylpentan-2-ol hydrochloride (32)



32 is obtained from 31 (448 mg, 1.12 mmol), α–chloroethyl chloroformate (0.48 ml, 4.47 mmol, 4eq) and polymer-supported Hünig's base (628 g, 2.23 mmol, 2eq) in DCM (10 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by preparative LCMS and conversion to its hydrochloride salt following *General Procedure 4* gives **32** as a white solid (0.11 g, 32%). MW 347.72; $C_{17}H_{26}FNO_3$. HCl. ^1H NMR (CD_3OD) δ_H 7.05-7.08 (1H, m), 6.95-6.98 (2H, m), 4.16 (1H, dd, 3 Hz, 12.5 Hz), 3.75- 3.86 (4H, m), 3.67 (1H, d, 10.5 Hz), 3.51 (1H, d, 12 Hz), 3.25-3.29 (1H, m), 3.07-3.20 (2H, m), 2.94 (2H, AB, 14 Hz), 1.86-1.9 (1H, m), 1.53 (1H, dd, 5.5 Hz, 14.5 Hz), 1.13 (1H, dd, 14.5 Hz, 5.5 Hz), 0.94 (3H, d, 2.5 Hz), 0.92 (3H, d, 2.5 Hz). LCMS (12 minute method): m/z 312.1 $[M-HCl+H]^+$, R_T 4.61 min.

Example 12: Preparation of 1-[2-(ethyloxy)phenyl]-4-methyl-2-morpholin-2-ylpentan-2-ol (34a, 34b)

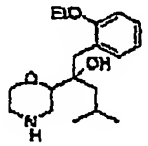
1-[2-(Ethyloxy)phenyl]-4-methyl-2-[4-(phenylmethyl)morpholin-2-ylpentan-2-ol (33)



Compound **33** is obtained from **6** (3.0 g, 11.5 mmol) and 2-ethoxybenzyl magnesium chloride (available from Reike Metals) (0.25M in diethyl ether, 50.5 ml, 12.6 mmol) in anhydrous THF (55 ml) following *General Procedure 2*. Another two equivalents of 2-ethoxybenzyl magnesium chloride (92 ml, 23 mmol) are added after 30 min. Purification

by automated column chromatography (0-25% EtOAc/n-heptane gradient) gives **33** (3.21 g) as a colourless oil in 86% purity as a mixture of diastereomers. MW 397.56; $C_{25}H_{35}NO_3$. LCMS (6 minute method): m/z 398.3 $[M+H]^+$, R_T 3.42 & 3.60 min.

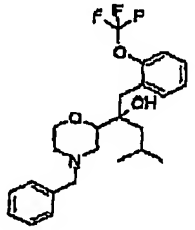
1-[2-(Ethyloxy)phenyl]-4-methyl-2-morpholin-2-ylpentan-2-ol (34a, 34b)



34a, 34b is obtained from **33** (3.20 mg, 8.06 mmol), α–chloroethyl chloroformate (3.48 ml, 32.2 mmol) and polymer-supported Hünig's base (4.53 g, 16.1 mmol) in DCM (100 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by automated column chromatography (5-40% MeOH/ DCM gradient), and preparative LCMS (gradient) gives **34a, 34b**. Chiral preparative chromatography (Heptane:EtOH:DEA 60:40:0.2 gradient, chiralcel-OD) afforded the first eluting enantiomer **34a** (13 mg) (RT 8.25 min), and the second eluting enantiomer **34b** (RT 10.17 min) as colourless oils. MW 307.44; $C_{18}H_{29}NO_3$. ^1H NMR ($CDCl_3$) δ_H 7.16-7.22 (2H, m), 6.84-6.93 (2H, m), 3.97-4.17 (2H, m), 3.90 (1H, dd, 3 Hz, 11 Hz), 3.53 (1H, td, 3 Hz, 11 Hz), 3.37 (1H, dd, 2 Hz, 10 Hz), 3.18 (1H, d, 12 Hz), 3.04 (1H, d, 14 Hz), 2.74-2.91 (4H, m), 1.89 (1H, septet, 6 Hz), 1.52 (1H, dd, 5.5 Hz, 14 Hz), 1.44 (3H, t, 7 Hz), 1.11 (1H, dd, 6 Hz, 14 Hz), 0.93 (3H, d, 7 Hz), 0.90 (3H, d, 7 Hz). LCMS (12 minute method): m/z 308.2 $[M-HCl+H]^+$, R_T 4.92 min.

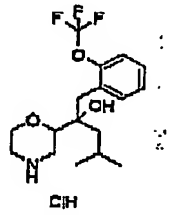
Example 13: Preparation of 4-methyl-2-morpholin-2-yl-1-{2[trifluoromethyl) oxy]phenyl}pentan-2-ol hydrochloride (36)

4-Methyl-2-[4-(phenylmethyl)morpholin-2-yl]-1-2[trifluoromethyl)oxy]phenyl} pentan-2-ol (35)



Compound 35 is prepared from 6 (0.83 g, 3.19 mmol) and commercially available (Fluorochem) 2-trifluoromethoxy benzyl magnesium bromide (0.5M solution in THF, 7.02 ml, 3.51 mmol, 1.1eq) in anhydrous THF (21 ml) following *General Procedure 2*. Further equivalents (3.19 ml, 1.60 mmol) of 2-trifluoromethoxy benzyl magnesium bromide are added after 30 min. Purification by ion exchange chromatography gives 35 as yellow oil (1.39 g, 99.5%). MW 437.51; $C_{24}H_{30}F_3NO_3$. LCMS (6 minute method): m/z 438.1 $[M+H]^+$, R_T 3.70 min.

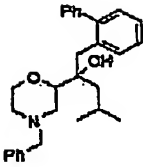
4-Methyl-2-morpholin-2-yl-1-{2[trifluoromethyl)oxy]phenyl}pentan-2-ol hydrochloride (36)



36 is obtained from 35 (1.39 g, 3.18 mmol), α–chloroethyl chloroformate (1.37 ml, 12.7 mmol, 4eq), and polymer-supported Hünig's base (1.79 g, 6.36 mmol, 2eq) in DCM (25 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by preparative LCMS (gradient) and conversion into the hydrochloride salt following *General Procedure 4* gives 36 (0.16 g, 14%) as foam. MW 383.82; $C_{17}H_{24}F_3NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.43 (1H, d, 7 Hz), 7.16-7.27 (3H, m), 4.05 (1H, dd, 3 Hz, 13 Hz), 3.58-3.74 (2H, m), 3.35-3.40 (1H, m), 3.23- 3.14 (1H, m), 2.97-3.10 (3H, m), 2.76 (1H, d, 14 Hz), 1.75 (1H, septet, 6.5 Hz), 1.42 (1H, dd, 6 Hz, 14.5 Hz), 0.98-1.11 (1H, m) 0.83 (3H, d, 6 Hz), 0.81 (3H, d, 6 Hz). LCMS (12 minute method): m/z 348.4 $[M-HCl+H]^+$, R_T 3.15 min.

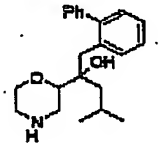
Example 14: Preparation of 1-[1,1'-Biphenyl]-2-yl-4-methyl-2-morpholin-2-ylpentan-2-ol hydrochloride (38)

2-(4-Benzyl-morpholin-2-yl)-1-biphenyl-2-yl-4-methyl-pentan-2-ol (37a, 37b)



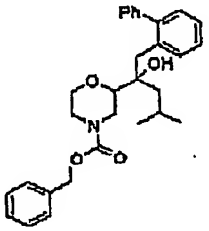
Compound 37 is prepared from 6 (2.5 g, 9.56 mmol) and 2-phenylbenzyl magnesium bromide (0.25M sol., 42.1 ml, 10.5 mmol, 1.1 eq) in anhydrous THF (21 ml) following *General Procedure 2*. 2-Phenylbenzyl magnesium bromide is prepared from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Another 3 equivalents of 2-phenylbenzyl magnesium bromide are added to drive the reaction to completion. Purification by automated column chromatography (0-25%, EtOAc/n-heptane, gradient) gives 37 (2.07g, 50%) which is used in the next step without further purification. MW 429.61; $C_{29}H_{35}NO_2$. FIA: m/z 430 $[M+H]^+$.

1-[1,1'-Biphenyl]-2-yl-4-methyl-2-morpholin-2-yl-pentan-2-ol (38a, 38b)



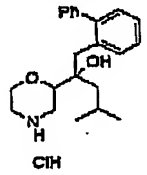
Compound 38 is obtained from 37 (2.07 g, 4.81 mmol), α-chloroethyl chloroformate (2.08 ml, 19.3 mmol) and polymer-supported Hünig's base (2.7 g, 9.6 mmol) in DCM (60 ml) following *General Procedure 3*. Purification by ion exchange chromatography, crystallization from MeOH/diethyl ether gives 38 as a white solid (738 mg, 45%). MW 339.48; $C_{22}H_{29}NO_2$. ^1H NMR ($CDCl_3$) δ_H 7.29-7.46 (8H, m), 7.23-7.28 (1H, m), 3.79-3.91 (2H, m), 3.66 (1H, dd, 10.9 Hz, 1.7 Hz), 3.18 (2H, dd, 12.8 Hz, 25.8 Hz), 2.84-3.04 (3H, m), 2.75 (1H, t, 11.5 Hz), 1.56-1.68 (1H, m), 1.22 (1H, dd, 5.65 Hz, 14.7 Hz), 0.98 (1H, dd, 5.65 Hz, 14.7 Hz), 0.81 (3H, d, 3.2 Hz), 0.78 (3H, d, 3.0 Hz). LCMS (12 minute method): m/z 340.3 $[M+H]^+$, R_T 5.62min.

Phenylmethyl-2-[1,1'-biphenyl]-2-ylmethyl)-1-hydroxy-3-methylbutyl] morpholine-4-carboxylate (cbz-38a, cbz-38b)



Benzyl chloroformate (0.37 ml, 2.61 mmol) is added to a stirring mixture of **38a,38b** (738 mg, 2.17 mmol) with $NaHCO_3$ (0.41 g) in a suspension of diethylether and water (24 ml) under N_2 at room temperature. After 1hour the reaction is quenched with ice water (15 ml) and diluted with DCM. The two phases are separated, the aqueous phase is further extracted DCM, the combined organic fractions are dried over magnesium sulphate, filtered and evaporated *in vacuo*. The isolated oil is purified using automated column chromatography (0-30% EtOAc/n-heptane gradient) followed by chiral preparative chromatography (Heptane:EtOH:DEA 35:65:0.2 gradient, chiracel AD-H) to give the first eluting enantiomer, **cbz-38a** (RT 2.61 min), and the second eluting enantiomer, **cbz-38b** (RT 2.99 min), both as a colourless oil. MW 473.62; $C_{30}H_{35}NO_4$. LCMS (6 minute method): m/z 456.3 $[M-H_2O+H]^+$ and 496.2 $[M+Na]^+$; R_T 5.34min.

1-[1,1'-Biphenyl]-2-yl-4-methyl-2-morpholin-2-ylpentan-2-ol hydrochloride (38a)

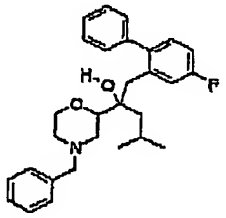


Palladium on carbon (10% weight) (0.4 g) is added to a stirring solution of **cbz-38a** (0.39 g, 0.84 mmol) with ammonium formate (0.53 g, 8.4 mmol) in ethanol (10 ml) at room temperature under nitrogen. The heterogeneous mixture is heated to reflux for 30 minutes, allowed to cool to room temperature and then filtered through a Celite pad. The filtrate is concentrated *in vacuo*, purified by ion exchange chromatography and then converted to the hydrochloride salt following *General Procedure 4* to give **38a** (0.25 g, 79%) as a yellow solid. MW 375.94; $C_{22}H_{29}NO_2.HCl$. ^1H NMR (CD_3OD) δ_H 7.48 (1H, bs), 7.11-7.33 (8H, m), 3.87(1H, bs), 3.37-3.57 (2H, m), 3.25 (1H, s), 2.77-3.10 (5H, m), 1.54 (1H,

s, br), 1.07-1.19 (1H, m), 0.93-1.00 (1H, m), 0.72 (3H, d, 6 Hz), 0.69 (3H, d, 6 Hz). LCMS (12 minute method): m/z 340.2 $[M+H]^+$, R_T 5.30min.

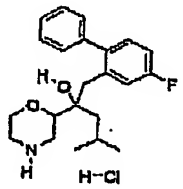
Example 15: Preparation of 1-(4-fluoro[1,1'-biphenyl]-2-yl)-4-methyl-2-morpholin-2-ylpentan-2-ol hydrochloride (40)

1-(4-Fluoro[1,1'-biphenyl]-2-yl-4-methyl-2-[4-(phenylmethyl)morpholin-2-yl]pentan-2-ol (39)



Compound 39 is prepared from 6 (0.95 g, 3.65 mmol) and 2-phenyl-5-fluoro benzyl magnesium bromide (0.5 M solution in diethyl ether, 1.2 eq) following *General Procedure 2*. 2-Phenyl-5-fluorobenzyl magnesium bromide is obtained from 2-phenyl-5-fluorobenzyl bromide following *General Procedure 5*. Excess 2-phenyl-5-fluoro benzyl magnesium bromide is subsequently added at room temperature and the reaction left stirring for 1 hour. Purification by flash column chromatography (EtOAc/cyclohexane 50 to 50%, gradient) gives 39 as a viscous oil (1.31 g, 80%). MW 447.60; $C_{29}H_{34}FNO_2$. LCMS: (6 minute method) m/z 448 $[M+H]^+$, R_T 3.88 min.

1-(4-Fluoro[1,1'-biphenyl]-2-yl)-4-methyl-2-morpholin-2-ylpentan-2-ol hydrochloride (40)

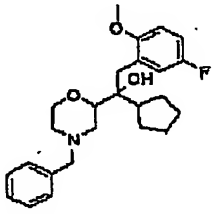


40 is prepared from 39 (1.31 g, 2.92 mmol), α-chloroethyl chloroformate (0.9 ml) and solid supported Hünig's base (1.64 g) in anhydrous DCM (30 ml) following *General Procedure 3*. Purification by ion exchange ion exchange chromatography gives the free base of 40 as a viscous oil (0.71 g, 62%). After further purification using UV-guided

preparative LCMS, the hydrochloride salt **40** (0.451 g, 39 %) is obtained following *General Procedure 4*. MW 393.95; $C_{22}H_{28}FNO_2$. HCl; ^{1}H NMR (DMSO-d_6): 9.16 (1H, s), 8.98 (1H, s), 7.44-7.32 (4H, m), 7.23-7.06 (4H, m), 3.83 (1H, dd, 12 Hz, 3 Hz), 3.59-3.50 (3H, m), 3.18 (1H, d, 12.5 Hz), 3.08 (1H, d, 12.5 Hz), 2.92-2.67 (4H, m), 1.54-1.40 (1H, m), 1.03 (1H, dd, 14.5 Hz, 5 Hz), 0.88 (1H, dd, 14.5 Hz, 6.5 Hz), 0.74 (3H, d, 6.5 Hz), 0.67 (3H, d, 6.5 Hz); LCMS: (12 min method) m/z 358 $[M\text{-}HCl+H]^+$ R_T 5.47 min.

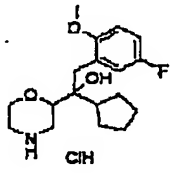
Example 16: Preparation of 1-cyclopentyl-2-[5-fluoro-2-(methyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (42)

1-Cyclopentyl-2-[5-fluoro-2-(methyloxy)phenyl]-1-[4-(phenylmethyl) morpholin-2-yl]ethanol (41)



Compound **41** is obtained from **7** (0.7 g, 2.56 mmol) and 2-methoxy-5-fluorobenzyl magnesium bromide (5.63 ml, 2.82 mmol 1.1eq) in anhydrous THF (15 ml) following *General Procedure 2*. Further equivalents of 2-methoxy-5-fluorobenzyl magnesium bromide (8.49 ml, 4.25 mmol) are added. Purification by ion exchange chromatography gives **41** as a yellow oil (843 mg, 62% purity). MW 413.54; $C_{25}H_{32}FNO_3$. LCMS (6 minute method): m/z 414.2 $[M+H]^+$@ R_T 4.11 min.

1-Cyclopentyl-2-[5-fluoro-2-(methyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (42)

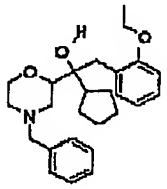


The free base of **42** is obtained from **41** (0.84 g, 2.04 mmol), α–chloroethyl chloroformate (0.88 ml, 8.16 mmol, 4eq) and polymer-supported Hünig's base (1.15 g,

4.08 mmol, 2eq) in DCM (15 ml) following *General Procedure 3*. Purification by ion exchange chromatography, followed by automated chromatography (5-20% DCM/MeOH gradient) and preparative LCMS and conversion into the hydrochloride salt following *General Procedure 4* gives 42 as a colourless gum (0.18 g, 14.1%). MW 359.82; $C_{18}H_{26}FNO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.11-7.14 (1H, m), 6.95-6.97 (2H, m), 4.07-4.15 (1H, m), 3.67-3.75 (2H, m), 3.43 (1H, d, 12 Hz), 3.23 (3H, s), 3.22 (1H, d, 12 Hz), 2.92-3.10 (4H, m), 2.13-2.19 (1H, m), 1.42-1.73 (8H, m). LCMS (12 minute method): m/z 324.1 $[M\text{-}HCl+H]^+$, RT 4.83min.

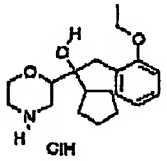
Example 17: Preparation of 1-cyclopentyl-2-[2-(ethyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (44)

1-Cyclopentyl-2-[2-(ethyloxy)phenyl]-1-[4-(phenylmethyl)morpholin-2-yl]ethanol (43)



Compound 43 is obtained from 7 (2.09 g, 7.68 mmol) and 2-ethyloxy benzyl magnesium bromide (available from Reike Metals) (0.25 M solution in diethyl ether, 1.1 eq) following *General Procedure 2*. Purification by preparative LCMS followed by preparative LCMS gives 43 as viscous oil (0.691 g, 22 %). MW 409.57; $C_{26}H_{35}NO_3$; LCMS: (6 min method) m/z 410 $[M+H]^+$, Rt 3.8min.

1-Cyclopentyl-2-[2-(ethyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (44)

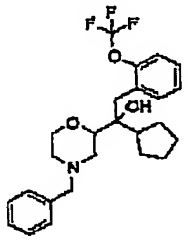


The free base of 44 is obtained from 43 (0.691 g, 1.69 mmol), α-chloroethyl chloroformate (0.80 ml) and solid supported Hünig's base (0.95 g) in anhydrous DCM following *General Procedure 3*. Purification by ion exchange and conversion into its hydrochloride salt following *General Procedure 4* gives 44 (0.39 g, 65%) MW 355.91;

$C_{19}H_{29}NO_3$.HCl; ^{1}H NMR (CD_3OD): 7.12-7.22 (2H, m), 6.82-6.88 (2H, m), 4.09-4.16 (3H, m), 3.69-3.80 (2H, m), 2.80-3.29 (6H, m), 2.04-2.10 (1H, m), 1.53-1.73 (11H, m); LCMS: (12 min method) m/z 320 $[M-HCl+H]^+$, Rt 5.03 min.

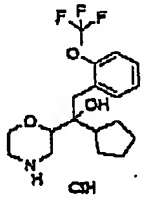
Example 18: Preparation of 1-Cyclopentyl-1-morpholin-2-yl-2-{2-(trifluoro methyl)oxy] phenyl} ethanol hydrochloride (46)

1-Cyclopentyl-2-{5-fluoro-2-(methyloxy)phenyl]-1-[4-(phenylmethyl) morpholin-2-yl]ethanol (45)



Compound 45 is obtained from 7 (0.6 g, 2.19 mmol) and commercially available (Fluorochem) 2-trifluoromethoxy-benzyl magnesium bromide (0.5M sol in diethylether, 4.8 ml, 2.41, mmol, 1.1 eq) in anhydrous THF (15 ml) following *General Procedure 2*. After addition of another 2 equivalents of 2-trifluoromethoxy-benzyl magnesium bromide and stirring for 2 hours at 0°C purification by ion exchange chromatography gives 45 (0.89g, 90%). MW 449.52; $C_{25}H_{30}F_3NO_3$. LCMS (6 minute method): m/z 450.2 $[M+H]^+$, R_T 4.084 min.

1-Cyclopentyl-1-morpholin-2-yl-2-{2-[(trifluoromethyl)oxy]phenyl} ethanol hydrochloride (46)

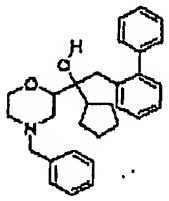


The free base of 46 is obtained from 45 (886 mg, 1.97 mmol), α-chloroethyl chloroformate (0.85 ml, 7.9 mmol, 4eq) and polymer-supported Hünig's base (1.11 g, 3.94 mmol, 2eq) in DCM (15 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by preparative LCMS (gradient) and conversion to its

hydrochloride salt following *General Procedure 4* gives **46** as a gum (140 mg, 20%). MW 359.36; $C_{18}H_{24}F_3NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.48-7.50 (1H, m), 7.14-7.25 (3H, m), 3.97 (1H, dd, 2.3 Hz, 12.5 Hz), 3.60-3.68 (2H, m), 3.27-3.31 (1H, m), 3.03 (2H, AB, 12.5 Hz), 2.73-2.97 (3H, m), 2.00-2.11 (1H, m), 1.30-1.63 (8H, m). LCMS (12 minute method): m/z 360.14 $[M-HCl+H]^+$, R_T 5.14 min.

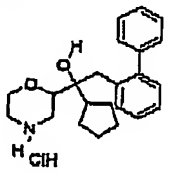
Example 19: Preparation of 2-[1,1'-biphenyl]-2-yl-1-cyclopentyl-1-morpholin-2-ylethanol hydrochloride (48)

2-[1,1'-Biphenyl]-2-yl-1-cyclopentyl-1-[4-(phenylmethyl)morpholin-2-yl]ethanol (47a,47b)



Compound **47** is prepared from **7** (1.27 g, 4.65 mmol) and 2-phenylbenzyl magnesium bromide (0.25 M solution in diethyl ether, 1.1 eq) following *General Procedure 2*. 2-Phenylbenzyl magnesium bromide is prepared from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Purification by flash column chromatography (eluent: cyclohexane/ethyl acetate/ 90/10 [v/v]) gives **47a,47b** as viscous oil (1.75 g). **47a,47b** is taken onto the next step without further purification. MW 441.62; $C_{30}H_{35}NO_2$. LCMS: (6 min method) m/z 442 $[M+H]^+$, R_T 3.51 min.

2-[1,1'-Biphenyl]-2-yl-1-cyclopentyl-1-morpholin-2-ylethanol hydrochloride (48a,48b)

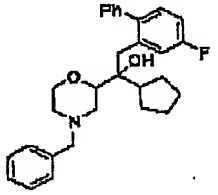


The free base of **48a, 48b** is prepared from **47a, 47b** (1.75 g, 3.95 mmol), solid supported Hünig's base (2.22 g) and α-chloroethyl chloroformate (1.62 ml) in anhydrous DCM (30 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by flash column chromatography (eluent: methanol/DCM 1/99 to 20/80

gradient) gives the free base as a viscous oil (805 mg, 58 %) which is converted into 48a, 48b following *General Procedure 4*. MW 387.95; $C_{23}H_{29}NO_2$.HCl; ^{1}H NMR (CD_3OD): 7.66-7.40 (1H, m) 7.19-7.47 (8H, m), 3.92 (1H, dd, 13 Hz, 3.5 Hz), 3.59-3.67 (2H, m), 3.05-3.16 (4H, m), 2.93 (1H, td, 13 Hz, 3.5 Hz,), 2.59 (1H, t, 12 Hz), 1.98-1.88 (1H, m), 1.55-1.19 (8H, m). LCMS: (12 min method) m/z 351 $[M-HCl+H]^+$, R_T 5.68 min.

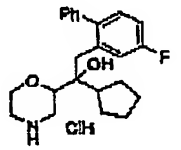
Example 20: Preparation of 1-cyclopentyl-2-(4-fluoro[1,1'-biphenyl]-2-yl)-1-morpholin-2-ylethanol hydrochloride (50)

1-Cyclopentyl-2-(4-fluoro[1,1'-biphenyl]-2-yl)-1-[4-(phenylmethyl)morpholin-2-ylethanol hydrochloride (49)



Compound 49 is obtained from 7 (0.9 g, 3.29 mmol) and 2-phenyl-5-fluorobenzyl magnesium bromide (0.5M solution in THF, 7.24 ml, 3.62 mmol) in anhydrous THF (20 ml) following *General Procedure 2*. 2-Phenyl-5-fluorobenzyl magnesium bromide is prepared from 2-phenyl-5-fluorobenzyl bromide following *General Procedure 5*. Further 2-phenyl-5-fluorobenzyl magnesium bromide is added after 30 min (0.3eq, 2 ml, 0.99 mmol). Purification by ion exchange chromatography followed by automated column chromatography (0-20% EtOAc/n-heptane gradient, 40 g) gives 49 (1.26 g, 83%) as a colourless liquid. MW 459.61; $C_{30}H_{34}FNO_2$. LCMS (6 minute method): m/z 460.5 $[M+H]^+$, R_T 3.98min.

1-Cyclopentyl-2-(4-fluoro[1,1'-biphenyl]-2-yl)-1-morpholin-2-ylethanol hydrochloride (50)

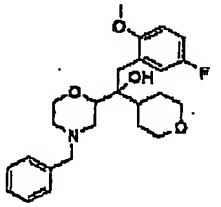


The free base of 50 is obtained from 49 (1.26 mg, 2.73 mmol), α-chloroethyl chloroformate (1.18 ml, 10.9 mmol) and polymer-supported Hünig's base (1.54 g, 5.47

mmol) in DCM (25 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by automated column chromatography (0-20% MeOH/ DCM gradient) and conversion to its hydrochloride salt gives **50** as a yellow solid (0.23 g, 23%). MW 405.94; $C_{23}H_{28}FNO_2.HCl$. ^1H NMR (CD_3OD) δ_H 7.20-7.37 (6H, m), 7.08-7.13 (1H, m), 6.91 (1H, td, 3.5 Hz, 8.5 Hz), 3.80 (1H, dd, 3.5 Hz, 13.0 Hz), 3.42-3.54 (2H, m), 2.99-3.06 (2H, m), 2.93 (2H, s), 2.83 (1H, td, 4.0 Hz, 12.5 Hz), 2.53 (1H, t, 12.0 Hz), 1.73-1.85 (1H, m), 1.12-1.44 (8H, m). LCMS (12 minute method): m/z 370.2 $[M-HCl+H]^+$, R_T 5.46min.

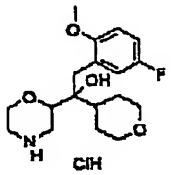
Example 21: Preparation of 2-[5-fluoro-2-methyloxy)phenyl]-1-morpholin-2-yl-1-tetrahydro-2H-pyran-4-ylethanol hydrochloride (52)

2-[5-Fluoro-2-(methyloxy)phenyl]-1-[4-(phenylmethyl)morpholin-2-yl]-1-tetrahydro-2H-pyran-4-ylethanol (51)



Compound **51** is obtained from **8** (0.6 g, 2.07 mmol) and 2-methoxy-5-fluorobenzyl magnesium bromide (4.6 ml, 2.28 mmol, 1.1eq) in anhydrous THF (15 ml) following *General Procedure 2*. Further equivalents of 2-methoxy-5-fluorobenzyl magnesium bromide (8.28 ml, 4.14 mmol) are added and the mixture is warmed to room temperature and left stirring over night. Purification by ion exchange chromatography followed by automated chromatography (10-70% n-heptane/EtOAc gradient) gives **51** as a colourless oil (375 mg, 42%). MW 429.54, $C_{25}H_{32}FNO_4$. LCMS (6 minute method): m/z 430.2 $[M+H]^+$, R_T 3.12 min.

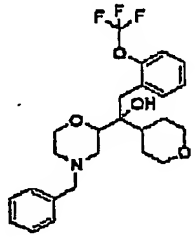
2-[5-Fluoro-2-methyloxy)phenyl]-1-morpholin-2-yl-1-tetrahydro-2H-pyran-4-ylethanol hydrochloride (52)



The free base of **52** is obtained from **51** (0.31 g, 0.73 mmol), α–chloroethyl chloroformate (0.31 ml, 2.9 mmol) and polymer-supported Hünig's base (0.41 g, 1.45 mmol) in DCM (7 ml) following *General Procedure 3*. Purification by ion exchange chromatography and conversion to the hydrochloride salt following *General Procedure 4* gives **52** as a white solid (0.19 g, 77%). MW 375.82; $C_{18}H_{26}FNO_4.HCl$. ^1H NMR (CD_3OD) δ_H 6.98-7.01 (1H, m), 6.83-6.86 (2H, m), 3.99 (1H,dd, 3.5 Hz, 13 Hz), 3.82-3.87 (2H, m), 3.63-3.73 (5H, m), 3.12-3.33 (4H, m), 2.91-3.02 (2H, m), 2.81 (2H, AB, 14 Hz), 1.31-1.73 (5H, m). LCMS (12 minute method): m/z 340.2 $[M-HCl+H]^+$, R_T 3.78 min.

Example 22: Preparation of 1-morpholin-2-yl-1-tetrahydro-2H-pyran-4-yl-2-{2-[(trifluoromethyl)oxyl phenyl}ethanol hydrochloride (54)

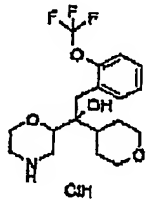
1-[4-(Phenylmethyl)morpholin-2-yl]-1-1-tetrahydro-2H-pyran-4-yl-2-{2-[(trifluoromethyl)oxy]phenyl}ethanol (53)



Compound **53** is obtained from **8** (0.61 g, 2.11 mmol) and commercially available (Fluorochem) 2-trifluoromethoxy benzyl magnesium bromide (4.6 ml, 2.32 mmol, 1.1eq) in anhydrous THF (15 ml) following *General Procedure 2*. A further half equivalent of 2-trifluoromethoxy benzyl magnesium bromide (4.22 ml, 2.11 mmol) is added. Purification by ion exchange chromatography gives **53** as an oil of 88% purity (1.39 g isolated

material) which is directly used in the next step. MW 465.52; $C_{25}H_{30}F_3NO_4$. LCMS (6 minute method): m/z 466.2 $[M+H]^+$, R_T 3.67 min.

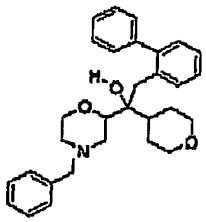
1-Morpholin-2-yl-1-tetrahydro-2H-pyran-4-yl-2-[2-[(trifluoromethyl)oxy] phenyl]ethanol hydrochloride (54)



The free base of **54** is obtained from **53** (0.27 g, 0.57 mmol), α–chloroethyl chloroformate (0.25 ml, 2.30 mmol, 4eq) and polymer-supported Hünig's base (0.32 g, 1.15 mmol, 2eq) in DCM (5 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by preparative LCMS (gradient) and conversion to the hydrochloride salt following *General Procedure 4* gives **54** as white solid (82 mg, 17%). MW 411.85; $C_{18}H_{24}F_3NO_4.HCl$. ^1H NMR (CD_3OD) δ_H 7.45-7.48 (1H, m), 7.16-7.27 (3H, m), 3.98 (1H, dd, 4.0 Hz, 13 Hz), 3.65-3.88 (4H, m), 3.12-3.31 (4H, m), 2.87-3.01 (4H, m), 1.30-1.68 (5H, m). LCMS (12 minute method): m/z 376.1 $[M+H]^+$, R_T 4.28 min.

Example 23: Preparation of 2-[1,1'-biphenyl]-2-yl-1-morpholin-2-yl-1-tetrahydro-2*H*-pyran-4-ylethanol hydrochloride (56)

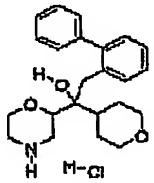
2-[1,1'-Biphenyl]-2-yl-1-[4-(phenylmethyl)morpholin-2-yl]-1-tetrahydro-2H-pyran-4-ylethanol (55)



Compound **55** is prepared from **8** (0.56 g, 1.94 mmol) and 2-phenyl benzyl magnesium bromide solution (0.25 M solution in diethyl ether, 9.31 ml, 2,33 mmol, 1.2 eq) following *General Procedure 2*. 2-Phenylbenzyl magnesium bromide is prepared from

commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Further 2-phenyl benzyl magnesium bromide solution (1 ml) is added and the reaction left under stirring overnight. Purification by ion exchange chromatography gives **55** as an off-white foam-like solid (0.37 g, 68 %). MW 457.62; $C_{30}H_{35}NO_3$. LCMS: (6 min method) m/z 458 $[M+H]^+$, R_T 3.58 min.

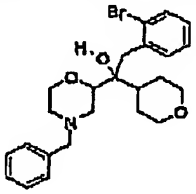
2-[1,1'-Biphenyl]-2-yl-1-morpholin-2-yl-1-tetrahydro-2H-pyran-4-ylethanol hydrochloride (56)



The free base of **56** is obtained from **55** (0.588 g, 1.28 mmol), solid supported Hünig's base (0.72 g) and α-chloroethyl chloroformate (0.53 ml) in anhydrous DCM (20 ml) following *General Procedure* 3. Purification by ion exchange chromatography gives the free base of **56** as viscous oil (0.483 g), contaminated with a small amount of the N-protected compound **55**. The residue is treated with an excess of reagents (1 eq), solid supported Hünig's base (0.36 g) and α-chloroethyl chloroformate (0.26 ml) in anhydrous DCM (20 ml) and methanol (20 ml) and purified by ion exchange chromatography to give the free base of **56** (0.432 g). Purification by preparative LCMS followed by conversion to its hydrochloride salt following *General Procedure 4* gives **56** (0.280 g, 54 %). MW 403.95; $C_{23}H_{29}NO_3$.HCl; ^{1}H NMR (CD_3OD): 7.45-7.59 (1H, m), 7.10-7.35 (8H, m), 3.85 (1H, dd, 13 Hz, 3.5 Hz), 3.75 (1H, dd, 11.5 Hz, 3.5 Hz), 3.51-3.59 (3H, m), 2.83-3.12 (7H, m), 2.64 (1H, t, 12 Hz), 1.36-1.52 (2H, m), 1.02-1.21 (2H, m), 0.90-0.94 (1H, m); LCMS: (12 min method) m/z 368 $[M-HCl+H]^+$, R_T 4.6 min.

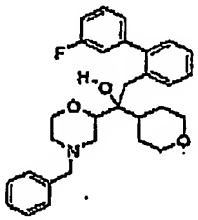
Example 24: Preparation of 2-(3'-Fluoro-biphenyl-2-yl)-1-morpholin-2-yl-1-(tetrahydro-pyran-4-yl)-ethanol (58)

2-Bromo-1-[4-(phenylmethyl) morpholin-2-yl]-1-(tetrahydro-pyran-4-yl)-ethanol



Commercially available (Aldrich) 2-bromobenzyl magnesium bromide (0.25M sol in diethylether, 48.9 ml, 12.18 mmol, 2.6 eq) is added in three portions over 90 minutes to a solution of 8 (1.35 g, 4.7 mmol) in dry THF (30 ml) at 0°C. After quenching with ice water, saturated ammonium chloride solution is added and the aqueous phase washed with EtOAc. The combined organic phases are washed with brine and water, dried over magnesium sulphate and solvents removed in vacuo. Purification by ion exchange chromatography followed by purification using automated column chromatography (10-50%, EtOAc/n-heptane gradient) gives 2-bromo-1-[4-(phenylmethyl) morpholin-2-yl]-1-(tetrahydro-pyran-4-yl)-ethanol (0.56 g, 26%). MW 460.42; C24H30BrNO3. LCMS (6 minute method): m/z 462.4 [M+H]+, RT 3.11 min.

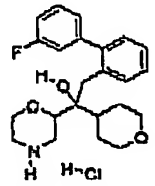
2-(3'-Fluoro-biphenyl-2-yl)-1-[4-(phenylmethyl) morpholin-2-yl]-1-(tetrahydro-pyran-4-yl)-ethanol (57)



To a suspension of Pd(OAc)2 (2.44 mg, 0.011 mmol, 0.02 eq) in acetonitrile (1.5 ml) is added triphenyl phosphine (11.4 mg, 0.043 mmol, 0.08 eq) under nitrogen at room temperature leading to the formation of a white precipitate. Addition of water (0.5 ml), 3-fluoro-phenyl boronic acid (91.2 mg, 0.65 mmol, 1.2 eq) and 2-bromo-1-[4-(phenylmethyl) morpholin-2-yl]-1-(tetrahydro-pyran-4-yl)-ethanol (0.25 mg, 0.54 mmol) gives a dark grey solution after 10-20 minutes which is heated up to reflux and left

stirring at reflux overnight. Further 3-fluoro-phenyl boronic acid (70 mg, 0.55 mmol, 1 eq) and Pd(OAc)2 (2-3 mg) is added and the mixture left stirring at reflux for another 24 hours. Purification by ion exchange chromatography gives 57 (0.21 g, 83%) MW 475.61; C30H34FNO3. LCMS (6 minute method): m/z 476.4 [M+H]+, RT 3.41min.

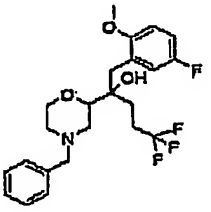
2-(3'-Fluoro-biphenyl-2-yl)-1-morpholin-2-yl-1-(tetrahydro-pyran-4-yl)-ethanol (58)



Compound 58 is obtained from 57 (0.213 g, 0.45 mmol), solid supported Hünig's base (0.25 g, 7.12 mmol, 4 eq) and α-chloroethyl chloroformate (0.19 ml, 1.79 mmol, 4 eq) in anhydrous DCM (7 ml) following *General Procedure* 3. Purification by ion exchange chromatography gives the free base of 58 as a white foam (125 mg) which is further purified by preparative liquid chromatography. Conversion to its hydrochloride salt following *General Procedure 4* gives 58 as a yellow gum (96.5 g, 56 %). MW 421.94; $C_{23}H_{28}FNO_3$.HCl. hydrochloride salt; ^{1}H NMR (CD_3OD): 7.60-7.45 (1H, m), 6.90-7.45 (6H, m), 3.55-3.95 (5H, m), 2.85-3.30 (10H, m), 2.64 (1H, t, 12.0 Hz), 0.95-1.45 (5H, m); LCMS: (12 min method) m/z 386 [M-hydrochloride salt+H]$^+$, Rt 4.64 min.

Example 25: Preparation of 5,5,5-trifluoro-1-(5-fluoro-2-methoxy-phenyl)-2-morpholin-2-yl-pentan-2-ol (60)

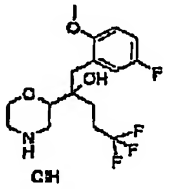
5,5,5-Trifluoro-1-[5-fluoro-2-(methyloxy)phenyl]-2-[4-(phenylmethyl) morpholin-2-yl]pentan-2-ol (59)



Compound 59 is obtained from 9 (0.7 g, 2.32 mmol) and 2-methoxy-5-fluorobenzyl magnesium bromide (5.11 ml, 2.55 mmol, 1.1eq) in dry THF (15 ml) following *General*

Procedure 2. Purification by ion exchange chromatography gives **59** as an oil of 80% purity which is directly used in the next step (0.9 g recovered material). MW 441.47; $C_{23}H_{27}F_4NO_4$. LCMS (6 minute method): m/z 442.4 $[M+H]^+$, R_T 3.36 min.

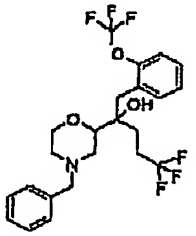
5,5,5-Trifluoro-1-[5-fluoro-2-(methyloxy)phenyl]-2-morpholin-2-yl]pentan-2-ol hydrochloride (60)



The free base of **60** is obtained from **59** (0.9 g, 2.04 mmol), α–chloroethyl chloroformate (0.88 ml, 8.15 mmol, 4eq) and polymer-supported Hünig's base (1.15 g, 4.08 mmol, 2eq) in DCM (25 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by preparative LCMS and conversion to the hydrochloride salt following *General Procedure 4* gives **60** as a yellow solid (0.133 g, 17%). MW 387.80; $C_{16}H_{21}F_4NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 6.93-6.96 (1H, m), 6.86-6.87 (2H, m), 4.09-4.13 (1H, m), 3.68-3.75 (4H, m), 3.42-3.47 (1H, m), 3.34-3.40 (1H, m), 3.16-3.25 (1H, m), 3.03-3.11 (2H, m), 2.83 (2H, AB, 14 Hz), 2.12-2.29 (2H, m), 1.58-1.68 (1H, m), 1.29-1.39 (1H, m). LCMS (12 minute method): m/z 352.1 $[M+H]^+$, R_T 4.54 and 4.66 2min.

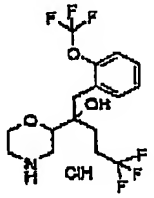
Example 26: Preparation of 5,5,5-trifluoro-2-morpholin-2-yl-1-(2-trifluoromethoxy-phenyl)-pentan-2-ol (62)

5,5,5-Trifluoro-2-[4-(phenylmethyl)morpholin-2-yl]-1{2-trifluoromethyl)oxy] phenyl}pentan-2-ol (61)



Compound **61** is obtained from **9** (0.7 g, 2.32 mmol) and commercially available (Fluorochem) 2-trifluoromethoxy benzyl magnesium bromide (5.12 ml, 2.56 mmol, 1.1eq) in dry THF (15 ml) following *General Procedure 2*. Purification by ion exchange chromatography followed by automated column chromatography (0-50% n-heptane/EtOAc gradient) gives **61** as an oil (0.27 g, 25%). MW 477.45; $C_{23}H_{25}F_6NO_3$. LCMS (6 minute method): m/z 478.4 $[M+H]^+$, R_T 3.63 min.

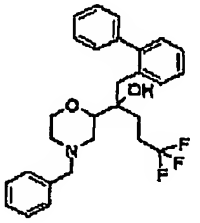
5,5,5-Trifluoro-2-morpholin-2-yl-1-{2-(trifluoromethyl)oxy]phenyl}pentan-2-ol hydrochloride (62)



The free base of **62** is obtained from **61** (0.25 g, 0.53 mmol), α-chloroethyl chloroformate (0.23 ml, 2.12 mmol, 4eq) and polymer-supported Hünig's base (0.30 g, 1.06 mmol, 2eq) in DCM (5 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by preparative LCMS and conversion to its hydrochloride salt gives **62** as a yellow solid (0.051 g, 23%). MW 423.78; $C_{16}H_{19}F_6NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.40-7.42 (1H, m), 7.19-7.30 (3H, m), 4.09-4.13 (1H, m), 3.71-3.78 (1H, m), 3.50-3.53 (1H, m), 3.36-3.40 (1H, m), 3.08-3.22 (3H, m), 2.89 (2H, AB, 14 Hz), 2.09-2.17 (2H, m), 1.65-1.75 (1H, m), 1.30-1.40 (1H, m). LCMS (12 minute method): m/z 388.1 $[M+H]^+$, R_T 4.99 min.

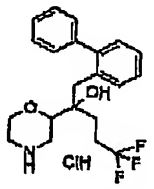
Example 27: Preparation of 1-[1,1'-biphenyl]-2-yl-5,5,5-trifluoro-2-morpholin-2-ylpentan-2-ol hydrochloride (64)

1-[1,1'-Biphenyl]-2-yl-5,5,5-trifluoro-2-[4-(phenylmethyl)morpholin-2-ylpentan-2-ol (63)



Compound **63** is obtained from **9** (0.7 g, 2.32 mmol) and 2-phenylbenzyl magnesium bromide (10.2 ml, 2.55 mmol, 1.1eq) in dry THF (15 ml) following *General Procedure 2*. 2-Phenylbenzyl magnesium bromide is prepared from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Purification by ion exchange chromatography followed by ISCO automated column chromatography (0-30% c-Hexane/EtOAc gradient) gives **63** as an oil (604mg, 60% purity). MW 469.55; $C_{28}H_{30}F_3NO_2$. LCMS (6 minute method): m/z 470.4 $[M+H]^+$, R_T 3.77 min.

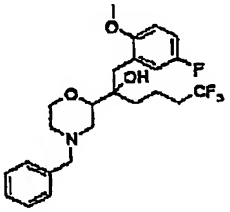
1-[1,1'-Biphenyl]-2-yl-5,5,5-trifluoro-2-morpholin-2-ylpentan-2-ol hydrochloride (64)



The free base of **64** is obtained from **63** (0.6 g, 1.29 mmol), α-chloroethyl chloroformate (0.56 ml, 5.15 mmol, 4eq) and polymer-supported Hünig's base (0.72 g, 2.58 mmol, 2eq) in DCM (12 ml) following *General Procedure 3*. Purification by ion exchange followed by preparative LCMS and conversion to the hydrochloride salt following *General Procedure 4* gives **64** as a yellow solid (0.16 g, 30%). MW 415.89; $C_{21}H_{24}F_3NO_2$. HCl. ^1H NMR (CD_3OD) δ_H 7.43-7.46 (1H, m), 7.18-7.35 (7H, m), 7.10-7.13 (1H, m), 3.90-3.95 (1H, m), 3.57-3.65 (1H, m), 3.34-3.38 (1H, m), 2.92 (2H, AB, 14.5 Hz), 2.88-3.13 (4H, m), 1.59-1.85 (2H, m), 1.15-1.39 (2H, m). LCMS (12 minute method): m/z 380.1 $[M+H]^+$, R_T 5.22 min.

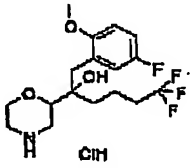
Example 28: Preparation of 6,6,6-trifluoro-1-[5-fluoro-2-(methyloxy)phenyl]-2-morphol-2-ylhexan-2-ol hydrochloride (66)

6,6,6-Trifluoro-1-[5-fluoro-2-(methyloxy)phenyl]-2-[4-phenylmethyl) morpholin-2-yl]hexan-2-ol (65)



Compound **65** is obtained from **10** (0.6 g, 1.90 mmol) and 2-methoxy-5-fluorobenzyl magnesium bromide (4.2 ml, 2.09 mmol, 1.1eq) in anhydrous THF (15 ml) following *General Procedure 2* (further 2-methoxy-5-fluorobenzyl magnesium bromide is added (3.8 ml, 1.90 mmol)). Purification by ion exchange chromatography gives **65** in 87% purity as an oil which is directly used in the next step (0.7 g of recovered material). MW 401.53; $C_{24}H_{32}FNO_3$. LCMS (6 minute method) m/z 456.2 $[M+H]^+$, R_T 3.5 6min.

6,6,6-Trifluoro-1-[5-fluoro-2-(methyloxy)phenyl]-2-morphol-2-ylhexan-2-ol hydrochloride (66)

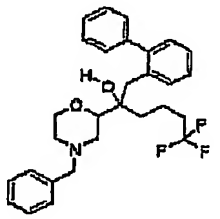


The free base of **66** is obtained from **65** (0.7 g, 1.53 mmol), α–chloroethyl chloroformate (0.66 ml, 6.1 mmol, 4eq) and polymer-supported Hünig's base (0.86 g, 3.05 mmol, 2eq) in DCM (13 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by automated column chromatography (0-20%MeOH/ DCM gradient) and conversion to the hydrochloride salt gives **66** (0.19 g, 40%) as a white solid. MW 401.83; $C_{17}H_{23}F_4NO_3.HCl$. ^1H NMR (CD_3OD) δ_H 7.04-7.08 (1H, m), 6.95-6.97 (2H, m), 4.21 (1H, dd, 3.0 Hz, 13.0 Hz), 3.78- 3.87 (4H, m), 3.63 (1H, dd, 2.0 Hz, 11.0 Hz), 3.45-3.49 (1H, m), 3.27-3.33 (1H, m), 3.12-3.21 (2H, m), 2.97 (2H, AB, 14.0 Hz), 1.97-

2.13 (2H,m), 1.61- 1.76 (2H, m), 1.48-1.58 (1H, m), 1.17-1.31 (1H, m). LCMS (12 minute method): m/z 366.1 $[M-HCl+H]^+$, R_T 4.72 min.

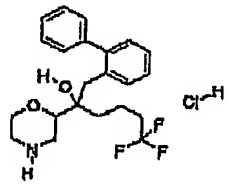
Example 29: Preparation of 1-[1,1'-biphenyl]-2-yl-6,6,6-trifluoro-2-morpholin-2-yl]hexan-2-ol hydrochloride (68)

1-[1,1'-Biphenyl]-2-yl-6,6,6-trifluoro-2-[4-(phenylmethyl)morpholin-2-yl]hexan-2-ol (67)



Compound 67 is prepared from 10 (0.853 g, 2.71 mmol) and 2-phenyl benzyl magnesium bromide (0.25 M solution in diethyl ether, 1.2 eq) following *General Procedure 2*. 2-Phenylbenzyl magnesium bromide is prepared from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Further 2-phenyl benzyl magnesium bromide is added later (19.2 ml, 4.8 mmol). Purification by flash column chromatography (eluent: EtOAc/cyclohexane 20/80 to 40/60 gradient), followed by ion exchange chromatography gives 67 as a viscous oil (369 mg, 28 %). MW 483.58; $C_{29}H_{32}NO_2F_3$. LCMS: (6 min method) m/z 484 $[M+H]^+$, R_T 4.26 min.

1-[1,1'-Biphenyl]-2-yl-6,6,6-trifluoro-2-morpholin-2-yl]hexan-2-ol hydrochloride (68)

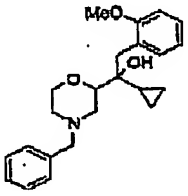


The free base of 68 is obtained from 10 (0.369 g, 0.76 mmol), solid supported Hünig's base (0.43 g) and α-chloroethyl chloroformate (0.32 ml) in anhydrous DCM (10 ml) following *General Procedure 3*. Purification by ion exchange chromatography gives the free base of 68 as a viscous oil (0.143 g, 48 %) which is converted into the hydrochloride salt 68 following *General Procedure 4*. MW 429.91; $C_{22}H_{27}NO_2F_3Cl$; ^1H NMR

(CD_3OD): 7.44-7.47 (1H, m), 7.16-7.35 (7H, m), 7.08-7.11 (1H, m), 3.94 (1H, dd, 12.5 Hz, 3.5 Hz), 3.57 (1H, t, 12.5 Hz), 3.34-3.38 (1H, m), 2.80-3.11 (6H, m), 1.65-3.90 (2H, m), 1.02-1.24 (4H, m). LCMS: (12 min method) m/z 394 $[M-HCl+H]^+$, Rt 5.42 min.

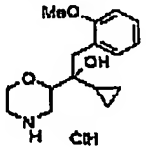
Example 30: Preparation of 1-Cyclopropyl-2-[-2-(methyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (70)

1-Cyclopropyl-2-[2-(methyloxy)phenyl]-1-[4-(phenylmethyl) morpholin-2-yl]ethanol (69)



Compound **69** is obtained from **77** (0.5 g, 2.04 mmol) and 2-methoxybenzyl magnesium bromide (available from Reike Metals) (0.25M solution in THF, 9.0 ml, 2.24 mmol, 1.1 eq.) in anhydrous THF (11 ml) following *General Procedure 1*. Further 2-methoxybenzyl magnesium bromide (0.25M solution in THF, 4.08 ml, 1.04 mmol, 0.5 eq.) is added after 10 minutes. Purification by ion exchange chromatography gives **69** in >90% purity which is directly used in the next step (0.706g, 94%). MW 367.49, $C_{23}H_{29}NO_3.HCl$. LCMS (6 minute method): m/z 368 $[M+H]^+$, R_T 2.52 min.

1-Cyclopropyl-2-[-2-(methyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (70)

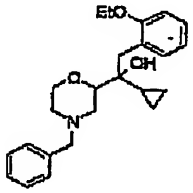


The free base of **70** is obtained from **69** (0.706 g, 1.92 mmol), α–chloroethyl chloroformate (0.83 ml, 7.69 mmol, 4 eq) and polymer-supported Hünig's base (1.08 g, 3.85 mmol, 2 eq) in DCM (25 ml) following *General Procedure 3*. Purification by ion exchange ion exchange chromatography followed by autaomated column chromatography (DCM/MeOH, 10-50% gradient) gives the free base of **70** (0.29g, 55%). A sample (0.06 g, 0.22 mmol) is converted into the hydrochloride salt **70** following *General Procedure 4* (0.063 g, 99%). MW 313.83; $C_{16}H_{23}NO_{3.HCl}$. ^1H NMR (CD_3OD) δ_H 6.95-7.15 (2H, m),

6.60-6.85 (2H, m), 3.95 (1H, dd, 2Hz, 10 Hz), 3.55-3.7 (2H, m), 3.15-3.4 (2H, m), 3.05 (3H, s), 2.7-3.95 (5H, m), 0.4-0.55 (1H, m), 0.15-0.3 (1H, m), -0.1-0.1 (3H, m). LCMS (12 minute method): m/z 278.1 $[M+H]^+$, R_T 3.81 min.

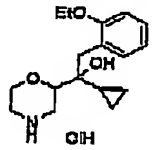
Example 31: Preparation of 1-Cyclopropyl-2-[-2-(ethyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (72)

1-Cyclopropyl-2-[2-(methyloxy)phenyl]-1-[4-(phenylmethyl) morpholin-2-yl]ethanol (71)



Compound **71** is obtained from **77** (0.36 g, 1.47 mmol) and 2-ethoxybenzyl magnesium bromide (available from Reike Metals) (0.25M solution in THF, 6.47 ml, 1.61 mmol, 1.1 eq) in anhydrous THF (8 ml) following *General Procedure 1*. Further 2-ethoxybenzyl magnesium bromide (0.25M solution in THF, 3.23 ml, 0.8 mmol, 0.5 eq.) is added after 30 minutes. Purification by ion exchange chromatography (0-40% EtOAc/n-heptane gradient) gives **71**. MW 382.52, $C_{24}H_{31}NO_3$.HCl. LCMS (6 minute method): m/z 382.4 $[M+H]^+$, R_T 2.83 min.

1-Cyclopropyl-2-[-2-(ethyloxy)phenyl]-1-morpholin-2-ylethanol hydrochloride (72)

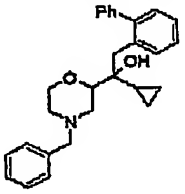


The free base of **72** is obtained from **71** (0.62 g, 1.62 mmol), α–chloroethyl chloroformate (0.93 g, 0.7 ml, 6.49 mmol, 4 eq.) and polymer-supported Hünig's base (0.91 g, 3.24 mmol, 2 eq) in DCM (20 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by automated column chromatography (DCM/MeOH, 10-50% gradient) gives the free base of **72** as an oil (0.32 g, 68%) in 89% purity. Conversion into the hydrochloride salt following *General Procedure 4* gives **72**. MW 327.85; $C_{17}H_{25}NO_3$.HCl. ^{1}H NMR (CD_3OD) δ_H 6.9-7.05 (2H, m), 6.60-6.8 (2H, m),

4.05 (1H, dd, 2Hz, 10 Hz), 3.7-3.85 (2H, m), 3.6 (1H, dt, 2 Hz , 7 Hz), 3.15-3.45 (2H, m), 2.8-2.95 (5H, m), 1.15 (3H, t, 7 Hz), 0.4-0.55 (1H, m), 0.15-0.3 (1H, m), -0.1-0.1 (3H, m). LCMS (12 minute method): m/z 292.1 $[M+H]^+$, R_T 4.44 min.

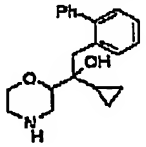
Example 32: Preparation of 2-[1,1'-biphenyl]-2-yl-1-cyclopropyl-1-morpholin-2-ylethanol hydrochloride (74)

2-[1,1'-Biphenyl]-2-yl-1-cyclopropyl-1-[4-(phenylmethyl)morpholin-2-yl]ethanol (73)



Compound 73 is obtained from 77 (0.7 g, 2.86 mmol) and 2-phenylbenzyl magnesium bromide (0.25M solution in THF, 12.58 ml, 3.15 mmol, 1.1 eq) in anhydrous THF (15 ml) following *General Procedure 1*. 2-Phenylbenzyl magnesium bromide is prepared from commercially available (Aldrich) 2-phenylbenzyl bromide following *General Procedure 5*. Further 2-phenylbenzyl magnesium bromide (0.25M solution in THF, 6.3 ml, 1.65 mmol, 0.5 eq.) is added after 30 minutes. Purification by ion exchange chromatography gives 73 as a gum (1.07 g, 91%). MW 413.56, $C_{28}H_{31}NO_2$.HCl. LCMS (6 minute method): m/z 414.4 $[M+H]^+$, R_T 3.11 min.

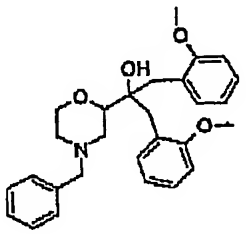
2-[1,1'-biphenyl]-2-yl-1-cyclopropyl-1-morpholin-2-ylethanol (74)



The free base of 74 is obtained from 73 (1.06 g, 2.57 mmol), α-chloroethyl chloroformate (1.11 ml, 10.3 mmol, 4 eq) and polymer-supported Hünig's base (1.44 g, 5.13 mmol, 2 eq) in DCM (30 ml) following *General Procedure 3*. Purification by ion exchange chromatography followed by automated column chromatography gives the free base of 74 (0.54 g, 65%) which is converted into the hydrochloride salt 74 following *General Procedure 4*. MW 323.44; $C_{21}H_{25}NO_2$. LCMS (12 minute method): m/z 324.2 $[M+H]^+$, R_T 4.96 min.

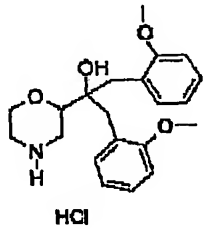
Example 33; Preparation of 1,3-Bis-(2-methoxy-phenyl)-2-morpholin-2-yl-propan-2-ol hydrochloride (79).

2-(4-benzyl-morpholin-2-yl)-1,3-bis-(2-methoxy-phenyl)-propan-2-ol (78)



Add a solution of 4-benzyl-morpholine-2-carboxylic acid ethyl ester (1.12 g, 4.49 mmol) in tetrahydrofuran (5 ml) to a stirred solution of 2-methoxybenzylmagnesium chloride (54 ml, 0.25 M solution in tetrahydrofuran, commercially available from Rieke Metals) at –10 °C under nitrogen atmosphere. After 1 hour, add a saturated aqueous solution of sodium bicarbonate and extract with diethyl ether. Combine the organic layers and extract with brine, dry over magnesium sulfate, filter, and concentrate under reduced pressure to give a residue to be taken forward without further purification. LCMS (m/e) = 448.2 (M+1) @ 4.8 minutes (12 minutes method).

1,3-Bis-(2-methoxy-phenyl)-2-morpholin-2-yl-propan-2-ol hydrochloride (79)

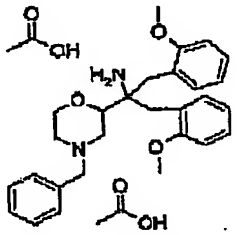


To a solution of 78 (2.2 g, 5 mmol) in EtOH (30 ml) under nitrogen atmosphere add ammonium formate (3.1 g, 50 mmol) followed by palladium on charcoal (10 %, 2.2 g). Stir and heat at reflux the resulting suspension for an hour. Allow the reaction mixture to cool to room temperature and then filter it through Celite ®. Wash the Celite ® with copious amounts of ethanol, combine the organic layers and concentrate under reduced pressure to obtain a residue. Purify and resolve the residue by Chiral HPLC to give 79: LCMS (m/e) = 358.1 (M+1) @ 4.6 minutes (12 minutes method) single major peak. δH

(300 MHz, DMSO D_6): 2.41-2.52 (m, 1H), 2.61-2.78 (m, 1H), 2.85-3.44 (m, 8H), 3.50-3.65 (m, 1H), 3.7 (s, 3H), 3.79 (s, 3H), 4.00-4.12 (m ,1H), 6.79-7.01 (m, 4H), 7.07-7.25 (m, 3H), 7.26-7.35 (m, 1H).

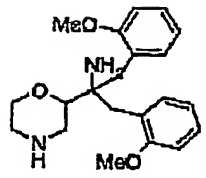
Example 34: Preparation of 1-(2-Methoxy-benzyl)-2-(2-methoxy-phenyl)-1-morpholin-2-yl-ethylamine dihydrochloride

1-(4-Benzyl-morpholin-2-yl)-1-(2-methoxy-benzyl)-2-(2-methoxy-phenyl)-ethylamine diacetate (80)



To a solution of 4-benzyl-morpholine-2-carbonitrile (10g, 49.5 mmol) in dry diethyl ether (100 ml) at –10 °C under an atmosphere of nitrogen is added a solution of 2-methoxybenzylmagnesium chloride (0.25M solution in tetrahydrofuran, (218 ml, 54.5 mmol) available from Aldrich Chemical Company or Rieke Metals) and the reaction mixture is further stirred at –10 °C for 30 minutes. Then the reaction is allowed to warm to room temperature and stirred overnight. The reaction is then cooled to 0 °C and quenched by addition of hydrochloric acid (5N aqueous solution, 50 ml) and the resulting mixture is stirred for 10 minutes at 0 °C. Next the solution is basified with sodium hydroxide (2N aqueous solution), filtered through Celite ® then extracted with diethyl ether, the organics collected, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a residue which is taken up into methanol and purified by SCX-2 chromatography prior to silica gel chromatography (0-40% ethyl acetate/hexane). The fractions containing the correct mass (FIA [M+H]+=447) are collected and purified via preparative HPLC to give **80** (72mg, 0.003%). LCMS (m/e)= 447.2 [M+H]+ @ 4.60 minutes (12 minutes method).

1-(2-Methoxy-benzyl)-2-(2-methoxy-phenyl)-1-morpholin-2-yl-ethylamine dihydrochloride (81)



2HCl

To a methanolic solution of **80** (70mg, 0.13 mmol) is added ammonium formate (100mg, 1.6 mmol) and 10% Pd-C (150mg). The reaction is stirred under nitrogen and heated at reflux for 30 minutes then cooled and filtered through Celite ®. The filtrate is concentrated *in vacuo* and the residue is taken up in methanol and purified by SCX-2 ® ion exchange resin and the resulting residue redissolved in a 2M hydrochloric acid in diethyl ether solution and then concentrated *in vacuo* to give **81** (1.7mg, 0. 3%). LCMS (m/e)= 357.2 [M+H]+ @ 2.07 minutes (12 minutes method). δH (300 MHz, CD_3OD): 2.65-3.02 (m, 6H), 3.05-3.16 (m, 1H), 3.24-3.41 (m, 2H), 3.52-3.65 (m, 1H), 3.70 (s, 3H), 3.80 (s, 3H), 3.91-4.05 (m, 1H), 6.84-7.08 (m, 4H), 7.12-7.32 (m, 4H).

The pharmacological profile of the present compounds may be demonstrated as follows. All of the exemplified compounds above have been found to exhibit a K_i value less than 1μm at the norepinephrine transporter as determined using the scintillation proximity assay described below. Furthermore, all of the exemplified compounds above have been found to inhibit the norepinephrine transporter to a greater extent than the serotonin and dopamine transporters using the scintillation proximity assays as described below.

Generation of stable cell-lines expressing the human dopamine, norepinephrine and serotonin transporters

Standard molecular cloning techniques are used to generate stable cell-lines expressing the human dopamine, norepinephrine and serotonin transporters. The polymerase chain reaction (PCR) is used in order to isolate and amplify each of the three full-length cDNAs from an appropriate cDNA library. Primers for PCR are designed using the following published sequence data:

Human dopamine transporter: GenBank M95167. Reference: Vandenbergh DJ, Persico AM and Uhl GR. *A human dopamine transporter cDNA predicts reduced glycosylation, displays a novel repetitive element and provides racially-dimorphic TaqI RFLPs.* Molecular Brain Research (1992) volume 15, pages 161-166.

Human norepinephrine transporter: GenBank M65105. Reference: Pacholczyk T, Blakely, RD and Amara SG. *Expression cloning of a cocaine- and antidepressant-sensitive human noradrenaline transporter.* Nature (1991) volume 350, pages 350-354.

Human serotonin transporter: GenBank L05568. Reference: Ramamoorthy S, Bauman AL, Moore KR, Han H, Yang-Feng T, Chang AS, Ganapathy V and Blakely RD. *Antidepressant- and cocaine-sensitivehuman serotonin transporter: Molecular cloning, expression, and chromosomal localization.* Proceedings of the National Academy of Sciences of the USA (1993) volume 90, pages 2542-2546.

The PCR products are cloned into a mammalian expression vector (eg pcDNA3.1 (Invitrogen)) using standard ligation techniques. The constructs are then used to stably transfect HEK293 cells using a commercially available lipofection reagent (Lipofectamine™ – Invitrogen) following the manufacture's protocol.

Scintillation proximity assays for determining the affinity of test ligands at the norepinephrine transporter.

The compounds of the present invention are norepinephrine reuptake inhibitors, and possess excellent activity in, for example, a scintillation proximity assay (e.g. J. Gobel, D.L. Saussy and A. Goetz, J. Pharmacol. Toxicolo. (1999), 42, 237-244). Thus ^{3}H-nisoxetine binding to norepinephrine re-uptake sites in a cell line transfected with DNA encoding human norepinephrine transporter binding protein is used to determine the affinity of ligands at the norepinephrine transporter.

Membrane Preparation:

Cell pastes from large scale production of HEK-293 cells expressing cloned human norepinephrine transporters are homogenized in 4 volumes 50mM Tris-HCl containing 300mM NaCl and 5mM KCl, pH 7.4. The homogenate is centrifuged twice (40,000g, 10min, 4°C) with pellet re-suspension in 4 volumes of Tris-HCl buffer containing the above reagents after the first spin and 8 volumes after the second spin. The suspended homogenate is centrifuged (100g, 10min, 4°C) and the supernatant kept and re-centrifuged (40,000g, 20min, 4°C). The pellet is resuspended in Tris-HCl buffer containing the above reagents along with 10%w/v sucrose and 0.1mM phenylmethylsulfonyl fluoride (PMSF). The membrane preparation is stored in aliquots (1ml) at −80°C until required. The protein concentration of the membrane preparation is determined using a bicinchoninic acid (BCA) protein assay reagent kit (available from Pierce).

[^{3}H]-Nisoxetine Binding Assay:

Each well of a 96 well microtitre plate is set up to contain the following:

50µl 2nM [N-methyl-^{3}H]-Nisoxetine hydrochloride (70-87Ci/mmol, from NEN Life Science Products)

75µl Assay buffer (50mM Tris-HCl pH 7.4 containing 300mM NaCl and 5mM KCl)

25µl Test compound, assay buffer (total binding) or 10µM Desipramine HCl (non-specific binding)

50µl Wheatgerm agglutinin coated poly (vinyltoluene) (WGA PVT) SPA Beads (Amersham Biosciences RPNQ0001) (10mg/ml)

50µl Membrane (0.2mg protein per ml)

The microtitre plates are incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results are analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki values for each of the test compounds.

Serotonin Binding Assay

The ability of a test compound to compete with [^{3}H]-citalopram for its binding sites on cloned human serotonin transporter containing membranes is used as a measure of test compound ability to block serotonin uptake via its specific transporter (Ramamoorthy, S., Giovanetti, E., Qian, Y., Blakely, R., (1998) J. Biol. Chem. 273, 2458).

Membrane Preparation:

Membrane preparation is essentially similar to that for the norepinephrine transporter containing membranes as described above. The membrane preparation is stored in aliquots (1ml) at –70°C until required. The protein concentration of the membrane preparation is determined using a BCA protein assay reagent kit.

[^{3}H]-Citalopram Binding Assay:

Each well of a 96 well microtitre plate is set up to contain the following:

50µl 2nM [^{3}H]-Citalopram (60-86Ci/mmol, Amersham Biosciences)

75µl Assay buffer (50mM Tris-HCl pH 7.4 containing 150mM NaCl and 5mM KCl)

25µl Diluted compound, assay buffer (total binding) or 100µM Fluoxetine (non-specific binding)

50µl WGA PVT SPA Beads (40mg/ml)

50µl Membrane preparation (0.4mg protein per ml)

The microtitre plates are incubated at room temperature for 10 hours prior to reading in a Trilux scintillation counter. The results are analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki (nM) values for each of the test compounds.

Dopamine Binding Assay

The ability of a test compound to compete with [^{3}H]-WIN35,428 for its binding sites on human cell membranes containing cloned human dopamine transporter has been used as a measure of the ability of such test compounds to block dopamine uptake via its specific transporter (Ramamoorthy et al 1998 *supra*).

Membrane Preparation:

Is essentially the same as for membranes containing cloned human serotonin transporter as described above.

[^{3}H]-WIN35,428 Binding Assay:

Each well of a 96well microtitre plate is set up to contain the following:

50µl 4nM [^{3}H]-WIN35,428 (84-87Ci/mmol, from NEN Life Science Products)

75µl Assay buffer (50mM Tris-HCl pH 7.4 containing 150mM NaCl and 5mM KCl)

25µl Diluted compound, assay buffer (total binding) or 100µM Nomifensine (non-specific binding)

50µl WGA PVT SPA Beads (10mg/ml)

50µl Membrane preparation (0.2mg protein per ml.)

The microtitre plates are incubated at room temperature for 120 minutes prior to reading in a Trilux scintillation counter. The results are analysed using an automatic spline fitting programme (Multicalc, Packard, Milton Keynes, UK) to provide Ki values for test compounds.

Acid Stability

The acid stability of a compound according to the present invention may be determined as a solution in buffer at 6 different pH values (HCl 0.1N, pH 2, pH 4, pH 6, pH 7, and pH 8) at 40°C over a time course of 72 hours. Samples may be taken at the beginning of the study and after 3, 6 and 24 hours and analysed by capillary electrophoresis. The original sample used in the study may contain 0.8% of the undesired epimer as internal standard. If the tested compound is chemically and configurationally stable under acidic conditions the samples taken at the different time points during the study should not show any significant change in the percentage of the undesired epimer.

In Vitro Determination of the Interaction of compounds with CYP2D6 in Human Hepatic Microsomes

Cytochrome P450 2D6 (CYP2D6) is a mammalian enzyme which is commonly associated with the metabolism of around 30% of pharmaceutical compounds. Moreover, this enzyme exhibits genetic polymorphism, resulting in the presence of both normal and poor metabolizers in the population. A low involvement of CYP2D6 in the metabolism of compounds (i.e. the compound being a poor substrate of CYP2D6) is desirable in order to reduce any variability from subject to subject in the pharmacokinetics of the compound. Also, compounds with a low inhibitor potential for CYP2D6 are desirable in order to avoid drug-drug interactions with co-administered drugs that are substrates of CYP2D6. Compounds may be tested both as substrates and as inhibitors of this enzyme by means of the following assays.

CYP2D6 substrate assay

Principle:

This assay determines the extent of the CYP2D6 enzyme involvement in the total oxidative metabolism of a compound in microsomes. Preferred compounds of the present invention exhibit less than 75% total metabolism via the CYP2D6 pathway.

For this in vitro assay, the extent of oxidative metabolism in human liver microsomes (HLM) is determined after a 30 minute incubation in the absence and presence of Quinidine, a specific chemical inhibitor of CYP2D6. The difference in the extent of metabolism in absence and presence of the inhibitor indicates the involvement of CYP2D6 in the metabolism of the compound.

Materials and Methods:

Human liver microsomes (mixture of 20 different donors, mixed gender) are acquired from Human Biologics (Scottsdale, AZ, USA). Quinidine and β–NADPH (β–Nicotinamide Adenine Dinucleotide Phosphate, reduced form, tetrasodium salt) are purchased from Sigma (St Louis, MO, USA). All the other reagents and solvents are of analytical grade. A stock solution of the new chemical entity (NCE) is prepared in a

mixture of Acetonitrile/Water to reach a final concentration of acetonitrile in the incubation below 0.5%.

The microsomal incubation mixture (total volume 0.1 mL) contains the NCE (4 µM), β–NADPH (1 mM), microsomal proteins (0.5 mg/mL), and Quinidine (0 or 2 µM) in 100 mM sodium phosphate buffer pH 7.4. The mixture is incubated for 30 minutes at 37 °C in a shaking waterbath. The reaction is terminated by the addition of acetonitrile (75 µL). The samples are vortexed and the denaturated proteins are removed by centrifugation. The amount of NCE in the supernatant is analyzed by liquid chromatography /mass spectrometry (LC/MS) after addition of an internal standard. A sample is also taken at the start of the incubation (t=0), and analysed similarly.

Analysis of the NCE is performed by liquid chromatography /mass spectrometry. Ten µL of diluted samples (20 fold dilution in the mobile phase) are injected onto a Spherisorb CN Column, 5 µM and 2.1 mm x 100 mm (Waters corp. Milford, MA, USA). The mobile phase consisting of a mixture of Solvent A/Solvent B, 30/70 (v/v) is pumped (Alliance 2795, Waters corp. Milford, MA, USA) through the column at a flow rate of 0.2 ml/minute. Solvent A and Solvent B are a mixture of ammonium formate 5.10^{-3} M pH 4.5/ methanol in the proportions 95/5 (v/v) and 10/90 (v/v), for solvent A and solvent B, respectively. The NCE and the internal standard are quantified by monitoring their molecular ion using a mass spectrometer ZMD or ZQ (Waters-Micromass corp, Machester, UK) operated in a positive electrospray ionisation.

The extent of CYP2D6 involvement (% of CYP2D6 involvement) is calculated comparing the extent of metabolism in absence and in presence of quinidine in the incubation.

The extent of metabolism without inhibitor (%) is calculated as follows:

$$\frac{(\text{NCE response in samples without inhibitor})_{\text{time 0}} - (\text{NCE response in samples without inhibitor})_{\text{time 30}}}{(\text{NCE response in samples without inhibitor})_{\text{time 0}}} \times 100$$

The extent of metabolism with inhibitor (%) is calculated as follows:

$$\frac{(\text{NCE response in samples without inhibitor})_{time\,0} - (\text{NCE response in samples with inhibitor})_{time\,30}}{(\text{NCE response in samples without inhibitor})_{time\,0}} \times 100$$

where the NCE response is the area of the NCE divided by the area of the internal standard in the LC/MS analysis chromatogram, time0 and time30 correspond to the 0 and 30 minutes incubation time.

The % of CYP2D6 involvement is calculated as follows :

$$\frac{(\%\text{ extent of metabolism without inhibitor}) - (\%\text{ extent of metabolism with inhibitor})}{\%\text{ extent of metabolism without inhibitor}} \times 100$$

CYP2D6 inhibitor assay

Principle:

The CYP2D6 inhibitor assay evaluates the potential for a compound to inhibit CYP2D6. This is performed by the measurement of the inhibition of the bufuralol 1'-hydroxylase activity by the compound compared to a control. The 1'-hydroxylation of bufuralol is a metabolic reaction specific to CYP2D6. Preferred compounds of the present invention exhibit an IC_{50} higher than 6 µM for CYP2D6 activity, the IC_{50} being the concentration of the compound that gives 50 % of inhibition of the CYP2D6 activity.

Material and methods:

Human liver microsomes (mixture of 20 different donors, mixed gender) are acquired from Human Biologics (Scottsdale, AZ). β–NADPH is purchased from Sigma (St Louis, MO). Bufuralol is purchased from Ultrafine (Manchester, UK). All the other reagents and solvents are of analytical grade.

Microsomal incubation mixture (total volume 0.1 mL) contains bufuralol 10 µM, β–NADPH (2 mM), microsomal proteins (0.5 mg/mL), and the new chemical entity (NCE) (0, 5, and 25 µM) in 100 mM sodium phosphate buffer pH 7.4. The mixture is incubated in a shaking waterbath at 37 °C for 5 minutes. The reaction is terminated by the addition of methanol (75 µL). The samples are vortexed and the denaturated proteins are removed by centrifugation. The supernatant is analyzed by liquid chromatography

connected to a fluorescence detector. The formation of the 1'-hydroxybufuralol is monitored in control samples (0 µM NCE) and in the samples incubated in presence of the NCE. The stock solution of NCE is prepared in a mixture of Acetonitrile/Water to reach a final concentration of acetonitrile in the incubation below 1.0%.

The determination of 1'hydroxybufuralol in the samples is performed by liquid chromatograhy with fluorimetric detection as described below. Twenty five µL samples are injected onto a Chromolith Performance RP-18e column (100 mm x 4.6 mm) (Merck KGAa, Darmstadt, Germany). The mobile phase, consisting of a mixture of solvent A and solvent B whose proportions change according the following linear gradient, is pumped through the column at a flow rate of 1 ml/min:

Time (minutes)	Solvent A (%)	Solvent B (%)
0	65	35
2.0	65	35
2.5	0	100
5.5	0	100
6.0	65	35

Solvent A and Solvent B consist of a mixture of 0.02 M potassium dihydrogenophosphate buffer pH3/ methanol in the proportion 90/10 (v/v) for solvent A and 10/90 (v/v) for solvent B. The run time is 7.5 minutes. Formation of 1'-hydroxybufuralol is monitored by fluorimetric detection with extinction at λ 252 nm and emission at λ 302 nm.

The IC_{50} of the NCE for CYP2D6 is calculated by the measurement of the percent of inhibition of the formation of the 1'-hydroxybufuralol in presence of the NCE compared to control samples (no NCE) at a known concentration of the NCE.

The percent of inhibition of the formation of the 1'-hydroxybufuralol is calculated as follows:

$$\frac{(1'\text{-hydroxybufuralol formed without inhibitor}) - (1'\text{-hydroxybufuralol formed with inhibitor})}{(1'\text{-hydroxybufuralol area formed without inhibitor})} \times 100$$

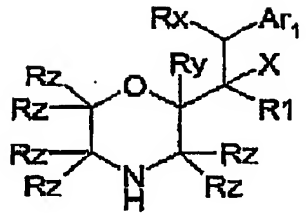
The IC_{50} is calculated from the percent inhibition of the formation of the 1'-hydroxybufuralol as follows (assuming competitive inhibition):

$$\frac{\text{NCE Concentration} \times (100 - \text{Percent of inhibition})}{\text{Percent of inhibition}}$$

The IC_{50} estimation is assumed valid if inhibition is between 20% and 80% (Moody GC, Griffin SJ, Mather AN, McGinnity DF, Riley RJ. 1999. Fully automated analysis of activities catalyzed by the major human liver cytochrome P450 (CYP) enzymes: assessment of human CYP inhibition potential. Xenobiotica, 29(1): 53-75).

CLAIMS

1. A compound of formula (I)



(I)

wherein,

X is OH, C1-C4 alkoxy, NH_2 or NH(C1-C4 alkyl);

Rx is H or C1-C4 alkyl;

Ry is H or C1-C4 alkyl;

each Rz group is independently H or C1-C4 alkyl, with the proviso that not more than 3 Rz groups may be C1-C4 alkyl;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C2-C6 alkenyl (optionally substituted with 1, 2 or 3 halogen atoms); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; C4-C7 cycloalkylalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH_2Ar2; and

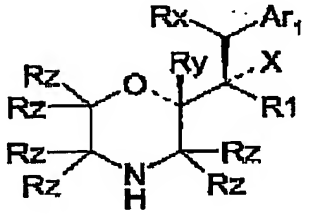
Ar1 and Ar2 are each independently a phenyl ring or a 5- or 6-membered heteroaryl ring each of which is optionally substituted with 1, 2 or 3 substituents (depending upon the number of available substitution positions) each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1,

2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy and/or with 1 substituent selected from pyridyl, thiophenyl, phenyl, benzyl and phenoxy each of which is optionally ring-substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R); and

each R is independently H or C1-C4 alkyl;

or a pharmaceutically acceptable salt thereof.

2. A compound of formula (II)



(II)

wherein, X, Rx, Ry, Rz, R1 and Ar1 are as defined for formula (I) in claim 1; or a pharmaceutically acceptable salt thereof.

3. A compound as claimed in any preceding claim wherein X is OH.

4. A compound as claimed in any preceding claim wherein Rx is H.

5. A compound as claimed in any preceding claim wherein Ry is H.

6. A compound as claimed in any preceding claim wherein each Rz is H.

7. A compound as claimed in any one of claims 1 to 6 wherein R1 is C1-C6 alkyl optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy

(optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy.

8. A compound as claimed in any one of claims 1 to 6 wherein R1 is C2-C6 alkenyl optionally substituted with 1, 2 or 3 halogen atoms.

9. A compound as claimed in any one of claims 1 to 6 wherein R1 is C3-C6 cycloalkyl optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond.

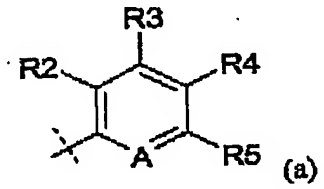
10. A compound as claimed in any one of claims 1 to 6 wherein R1 is C4-C7 cycloalkylalkyl optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond.

11. A compound as claimed in any one of claims 1 to 6 wherein R1 is CH_2Ar2 wherein Ar2 is a phenyl ring or a 5- or 6-membered heteroaryl ring each of which is optionally substituted with 1, 2 or 3 substituents (depending upon the number of available substitution positions) each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy and/or with 1 substituent selected from pyridyl, thiophenyl, phenyl, benzyl and phenoxy each of which is optionally ring-substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R.

12. A compound as claimed in any preceding claim wherein Ar1 is a phenyl ring or a 5- or 6-membered heteroaryl ring; each of which is substituted in the *ortho* position with

a substituent selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo, hydroxy, pyridyl, thiophenyl, phenyl, benzyl and phenoxy, each of which *ortho* substituents is optionally ring-substituted (where a ring is present) with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R; and each of which is (in addition to *ortho* substitution) optionally further substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy.

13. A compound as claimed in any preceding claim wherein Ar1 is a group of the formula (a):



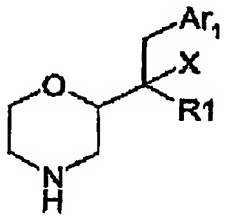
(a)

wherein,

A is N or CR6 (preferably CR6); R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo, hydroxy, pyridyl, thiophenyl, phenyl (optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), or C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms)) or phenoxy (optionally substituted with 1, 2 or 3 halogen atoms); R3 is H; R4 is H; R5 is H, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally

substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo or hydroxy; and R6 (if present) is H.

14. A compound of formula (III)



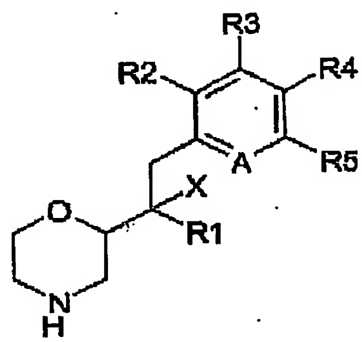
(III)

wherein, X, R1 and Ar1 are as defined for formula (I) in claim1; or a pharmaceutically acceptable salt thereof.

15. A compound according to claim 14 wherein
X is OH or NH_2;
R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkylthio (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkoxy, C1-C4 alkylsulfonyl, cyano, -CO-O(C1-C2 alkyl), -O-CO-(C1-C2 alkyl) and hydroxy); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C, S-C or C=C bond; or CH_2Ar2 wherein Ar2 is a phenyl ring or a pyridyl (preferably 2-pyridyl) ring each of which may be substituted with 1, 2 or 3 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy; and
Ar1 is a phenyl ring or a 5- or 6-membered heteroaryl ring; each of which is substituted in the *ortho* position with a substituent selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -

CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo, hydroxy, pyridyl, thiophenyl, phenyl, benzyl and phenoxy, each of which *ortho* substituents is optionally ring-substituted (where a ring is present) with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), carboxy, nitro, hydroxy, cyano, -NRR, -CONRR, SO_2NRR and SO_2R; and each of which is (in addition to *ortho* substitution) optionally further substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), -CO-O(C1-C4 alkyl), cyano, -NRR, -CONRR, halo and hydroxy; or a pharmaceutically acceptable salt thereof.

16. A compound of formula (IV)



(IV)

wherein,

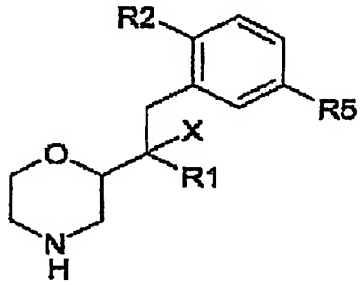
X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms), cyano, and hydroxy); C3-C6 cycloalkyl (optionally substituted with 1, 2 or 3 halogen atoms and/or with 1 substituent selected from C1-C4 alkoxy and hydroxy) wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond; or CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted with 1, 2 or 3 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1,

2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy;

A is N or CR6 (preferably CR6); R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo, hydroxy, pyridyl, thiophenyl, phenyl (optionally substituted with 1, 2 or 3 substituents each independently selected from halogen, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), or C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms)) or phenoxy (optionally substituted with 1, 2 or 3 halogen atoms); R3 is H; R4 is H; R5 is H, C1-C4 alkyl (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), C1-C4 alkylthio (optionally substituted with 1, 2 or 3 halogen atoms), halo or hydroxy; and R6 (if present) is H; or a pharmaceutically acceptable salt thereof.

17. A compound of formula (V)



(V)

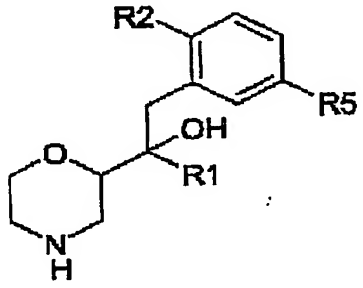
wherein,

X is OH or NH_2;

R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C3-C6 cycloalkyl wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond or CH_2Ar2 wherein Ar2 is a phenyl ring optionally substituted with 1 or 2 substituents each independently selected from C1-C4 alkyl (optionally substituted with 1,

2 or 3 halogen atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 halogen atoms), halo and hydroxy;
R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms) or phenyl (optionally substituted with 1, 2 or 3 fluorine atoms); and R5 is H or F; or a pharmaceutically acceptable salt thereof.

18. A compound of formula (VI)



(VI)

wherein,
R1 is C1-C6 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms) or C3-C6 cycloalkyl wherein one C-C bond within the cycloalkyl moiety is optionally substituted by an O-C bond;
R2 is C1-C4 alkyl (optionally substituted with 1, 2 or 3 fluorine atoms), C1-C4 alkoxy (optionally substituted with 1, 2 or 3 fluorine atoms) or phenyl (optionally substituted with 1, 2 or 3 fluorine atoms); and R5 is H or F; or a pharmaceutically acceptable salt thereof.

19. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent, excipient or carrier

20. A compound as claimed in any one of claims 1 to 18 for use in therapy.

21. A compound as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof for use as an inhibitor of the reuptake of norepinephrine.

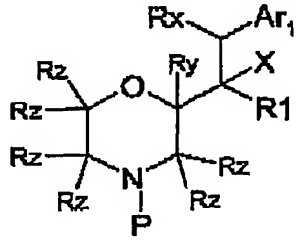
22. A compound as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof for treating disorders associated with norepinephrine dysfunction in mammals.

23. The use of a compound as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of disorders associated with norepinephrine dysfunction in mammals.

24. A method for inhibiting the reuptake of norepinephrine in mammals comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof.

25. A method for treating disorders associated with norepinephrine dysfunction in mammals comprising administering to a patient in need thereof an effective amount of a compound as claimed in any one of claims 1 to 18 or a pharmaceutically acceptable salt thereof.

26. A process for the preparation of a compound of formula (I) comprising the step of deprotecting a compound of the formula (XIV)

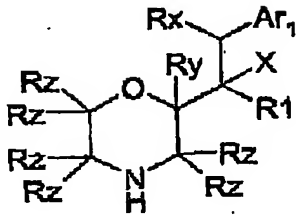


(XIV)

wherein P represents an N-protecting group and all other variables are as defined for formula (I) in claim 1, to provide a compound of formula (I), optionally followed by the step of forming a pharmaceutically acceptable salt.

ABSTRACT

Compounds of the general formula (I)



(I)

are inhibitors of the reuptake of norepinephrine. As such, they may be useful for the treatment of disorders of the central and/or peripheral nervous system.